

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 03/015799 A1

(51) International Patent Classification⁷: A61K 31/737, 31/42, 31/501, 31/415, A61P 29/00 // (A61K 31/737, 31:42) (A61K 31/737, 31:50) (A61K 31/737, 31:501) (A61K 31/737, 31:415)

(21) International Application Number: PCT/US02/25673

(22) International Filing Date: 13 August 2002 (13.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/312,211 14 August 2001 (14.08.2001) US
10/215,539 9 August 2002 (09.08.2002) US

(71) Applicant (for all designated States except US): PHARMACIA CORPORATION [US/US]; Corporate Patent Department, 800 North Lindbergh Boulevard, Mail Zone O4E, St. Louis, MO 63167 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PULASKI, Steven, P. [US/US]; 4 Thoroughbred Drive, Branchburg, NJ 08876 (US). KUNDEL, Susan [US/CH]; Saint Alban Anlage 25, CH-4052 Basel (CH).

(74) Agents: WARNER, James, M. et al.; Pharmacia Corporation, Corporate Patent Department, 800 North Lindbergh Boulevard, Mail Zone O4E, St. Louis, MO 63167 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/015799 A1

(54) Title: COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF PAIN AND INFLAMMATION WITH A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND CHONDROITIN SULFATE

(57) Abstract: A method of treating, preventing, or inhibiting pain, inflammation or inflammation-associated disorder in a subject in need of such treatment or prevention provides for treating the subject with chondroitin sulfate and a cyclooxygenase-2 selective inhibitor, or a prodrug thereof, wherein the amount of chondroitin sulfate and the amount of a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof together constitute a pain or inflammation suppressing treatment or prevention effective amount. Glucosamine can optionally be present. Compositions that contain the combination of chondroitin sulfate and cyclooxygenase-2 selective inhibitor and, optionally, the glucosamine, are disclosed, as are pharmaceutical compositions.

(10) 6,156,781 (substituted pyrazolyl benzenesulfonamides), (11) 6,110,960 (for dihydrobenzopyran and related compounds).

The identity, efficacy and side effects of new cyclooxygenase-2 selective inhibitors for the treatment of inflammation have been reported.

- 5 Exemplary references include: (1) Hillson, J. L. *et al.*, *Expert Opin. Pharmacother.*, 1(5):1053-66 (2000), (for rofecoxib, Vioxx®, Merck & Co., Inc.), (2) Everts, B. *et al.*, *Clin. Rheumatol.*, 19(5):331-43 (2000), (for celecoxib, Celebrex®, Pharmacia Corporation, and rofecoxib), (3) Jamali, F., *J. Pharm. Pharm. Sci.*, 4(1):1 - 6 (2001), (for celecoxib), (4) U.S. Patent Nos. 5,521,207 and 5,760,068 (for substituted pyrazolyl benzenesulfonamides), (5) Davies, N. M. *et al.*, *Clinical Genetics*, Abstr. at <http://www.mmhc.com/cg/articles/CG0006/davies.html> (for meloxicam, celecoxib, valdecoxib, parecoxib, deracoxib, and rofecoxib); <http://www.celebrex.com> (for celecoxib), (6)
- 10 (15) <http://www.docguide.com/dg.nsf/PrintPrint/F1F8DDD2D8B009408525698F00742187>, 5/9/2001 (for etoricoxib, MK-663, Merck & Co., Inc.), (7) Saag, K. *et al.*, *Arch. Fam. Med.*, 9(10):1124 - 34 (2000), (for rofecoxib), (8) International Patent Publication No. WO 00/24719 (for ABT 963, Abbott Laboratories).

20 Although cyclooxygenase-2 selective inhibitors recently have been targets of intense research in the area of treatment and prevention of inflammation, especially related to arthritis treatment, other compounds have also been reported to be useful for anti-inflammatory applications. For example, orally administered chondroitin sulfate has been reported to

25 have a tropism for cartilaginous tissues in rats and for knee tissues in humans, and to significantly decrease granuloma formation due to sponge implants in rats. Palmieri, L. *et al.*, *Osteoarthritis Cartilage*, 6(Suppl. A):14 - 21 (1998). Soll *et al.* in U. S. Patent No. 5,498,606 described a method of protecting or ameliorating a human or animal joint cavity from the effects

30 of trauma -- such as inflammation -- by injecting chondroitin sulfate into the joint cavity. Direct injection into a joint was also described in European Patent Application EP 0 911 025 A1, where microcapsules containing a

high molecular weight biodegradable and biocompatible material and a drug were reported to be useful for treatment of arthropathy. Meloxicam was one of many materials that could be used as the drug. It was reported that when the preparation was used in the form of an injection, the 5 microcapsules could be suspended in a dispersion medium, which could contain hyaluronic acid, chondroitin sulfate, or salts thereof.

In European Patent Application EP 0 855 179 A2, it was reported that coated capsules containing a liposome powder encapsulating a drug were useful to improve the oral bioavailability of difficult-to-absorb drugs. 10 Chondroitin-4-sulfate and chondroitin-6-sulfate were listed among a large number of potential drugs that could be encapsulated according to the described method, as was nimesulide. There was no mention, however, of any mixtures of the drugs.

Glucosamine is another compound that has been reported to be 15 beneficial in the treatment of osteoarthritis. See, e.g., Walker-Bone, K. *et al.*, *BMJ* 322:673 (2001). See, e.g., Creamer, P., *Curr. Opin. Rheumatol.*, 12(5):450-5 (2000). See, e.g., McAlindon, T. E. *et al.*, *JAMA* 283(11):1469-75 (2000). N-acetylglucosamine has been reported by Shikhman, A. R. *et al.*, in *J. Immunol.*, 166(8):5155-60 (2001), to prevent il- 20 1beta-mediated activation of human chondrocytes to result in anti- inflammatory activity. Rubin, B. R. *et al.*, in *Adv. Chitin Sci.*, 4(EUCHIS'99):266-269 (2000), reported the use of N-acetyl-D- glucosamine as a sustained release source of glucosamine. The long- 25 term effects of glucosamine sulfate on osteoarthritis progression was reported by Reginster, J. Y. *et al.*, in *Lancet*, 357:251-6 (2001). This group reported that a group of patients with knee osteoarthritis had no significant joint-space loss in 3 years when taking 1500 mg/day of glucosamine sulfate. A comment on the article by McAlindon, T., *Lancet*, 357(9252):247-8, suggested that health care professionals should 30 accommodate the possibility that a nutritional supplement, such as glucosamine, may have valuable therapeutic effects for osteoarthritis.

Combinations of glucosamine with other materials have also been reported to be useful for the treatment of arthritis and inflammation. In WO 00/74696, Zhong *et al.*, discussed the use of glucosamine and at least one Chinese herb selected from *Tripterygium wilfordii*, *Ligustrum lucidum* and *Erycibe schmidii* for alleviating the symptoms of an ailment that involves the inflammation or degeneration of joint tissues, such as arthritis. The publication speculated that both *Ligustrum lucidum* and *Tripterygium wilfordii* could affect the activity of the Cox-2 enzyme. It is known, however, that the triterpenoids, ursolic acid and oleanic acid, which are the enzyme inhibitory compounds of *Ligustrum lucidum* extracts, are not substantially more selective for the inhibition of Cox-2 than for Cox-1. See, for example, Ringbom, T. *et al.*, *J. Nat. Prod.*, 61(10):1212 - 1215 (1998). Furthermore, it is known that extracts of *Tripterygium wilfordii* act primarily by suppressing the expression of Cox-2 mRNA, rather than by inhibiting the activity of the Cox-2 enzyme. See, Tao, X. *et al.*, *Arthritis Rheum.*, 41(1):130 - 138 (1998); Maekawa, K. *et al.*, *Inflamm. Res.*, 48(11):575 - 581 (1999); and Tao, X. *et al.*, *Inflamm. Res.*, 48(3):139 - 148 (1999), among others.

The combination of chondroitin sulfate with glucosamine, with or without the presence of other materials, was described by Towheed, T. E. *et al.*, in *JAMA* 283(11):1483-1484 (2000). The same combination was reported by Canapp, S.O. *et al.*, in *Am. J. Vet. Res.*, 60(12):1552 - 7 (1999), who believed that orally administered glucosamine hydrochloride and chondroitin sulfate had a protective effect against chemically induced synovitis and associated bone remodeling in dogs. U.S. Patent Nos. 6,162,787; 6,136,795; 5,929,050; 5,916,565; 5,888,514; 5,840,715; 4,772,591; and 4,473,551, also report glucosamine combinations with chondroitin sulfate. Henderson, R. W., in WO 9827988 described an aminosugar and glycosaminoglycan composition for the treatment and repair of connective tissue. A commercial dietary supplement, Flex-A-Min®, is reported to provide a combination of glucosamine, chondroitin

sulfate and methylsulfonylmethane, and is directed at subjects with arthritis and joint pain.

5 Labeled chondroitin sulfate and glucosamine have also been widely used for the measurement of proteoglycan metabolism. For example, the effect of meloxicam, aceclofenac and diclofenac on the metabolism of newly synthesized proteoglycan and hyaluronan in osteoarthritic cartilage explants was studied by Blot *et al.*, *Br. J. Pharmacol.*, 131(7):1413-1421 (2000), by *in vitro* administration of each of the NSAIDs to the explants. Similar uses for glucosamine have been reported in Sasaki, T. *et al.*, *J. Appl. Physiol.*, 66(2):764-70 (1989), among others.

10 Even though the treatment and prevention of pain and inflammation, such as is caused by arthritis and other inflammation-associated disorders, has advanced very significantly during the past several years, there still remains a need for improved methods and 15 compositions that prevent and/or treat pain and inflammation, and particularly for methods and compositions that are efficacious for such applications in physiologically acceptable dosages, and which are selective in their physiological impact.

SUMMARY OF THE INVENTION

20 Briefly, therefore the invention is directed to a novel method for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering chondroitin sulfate and a cyclooxygenase-2 selective inhibitor or prodrug thereof to the subject.

25 The invention is also directed to a novel method for the treatment of a subject that has need of the treatment or prevention of disorders having an inflammatory component, the method comprising administering to the subject a therapeutically effective dose of chondroitin sulfate and cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt 30 or prodrug thereof. In one embodiment, of the novel method, glucosamine is also present.

The invention is also directed to a novel composition for the treatment, prevention, or inhibition of pain, inflammation, or inflammation-associated disorder comprising chondroitin sulfate and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

5 The invention is also directed to a novel pharmaceutical composition comprising chondroitin sulfate; a cyclooxygenase-2 specific inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically-acceptable excipient.

10 The invention is also directed to a novel kit that is suitable for use in the treatment, prevention or inhibition of pain, inflammation or inflammation-associated disorder, the kit comprises a first dosage form comprising chondroitin sulfate and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder. Optionally, the kit can also contain a third dosage form comprising glucosamine.

15

20 Several advantages are achieved by the present invention, including the provision of an improved method and a composition that prevent and/or treat pain and/or inflammation, and also a method and a composition that are efficacious for such applications in physiologically acceptable dosages, and which are selective in their physiological impact.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

25 In accordance with the present invention, it has been discovered that pain, inflammation and inflammation-associated disorders can be prevented and/or treated in subjects that are in need of such prevention or treatment by treating the subject with a combination of chondroitin sulfate and a cyclooxygenase-2 selective inhibitor. Optionally, glucosamine can also be present in the combination.

30 The amount of the chondroitin sulfate and the amount of the cyclooxygenase-2 selective inhibitor that are used in the treatment are selected so that together they constitute a pain or inflammation

5 suppressing treatment or prevention effective amount. In those embodiments where glucosamine is present, the amount of glucosamine is selected so that the when it is used in combination with the cyclooxygenase-2 selective inhibitor and the chondroitin sulfate, a dosage of the combination provides a pain or inflammation suppressing treatment or prevention effective amount.

10 The novel method of treating a subject with a combination of chondroitin sulfate and a cyclooxygenase-2 selective inhibitor provides a safe and efficacious method for preventing and alleviating pain and inflammation and for preventing and treating inflammation-associated disorders. In addition to being an efficacious method and composition for preventing and/or alleviating pain and inflammation in a treated subject, such method and composition might also provide desirable properties such as stability, ease of handling, ease of compounding, lack of side 15 effects, ease of preparation or administration, and the like.

The novel method and compositions comprise the use of chondroitin sulfate and a cyclooxygenase-2 selective inhibitor.

20 The chondroitin sulfate that is useful in the present method and compositions is a glycosaminoglycan having N-acetylchondrosine as a disaccharide repeating unit. The chondroitin sulfate can supplied by any material that contains chondroitin sulfate A (an alternating copolymer of β -glucuronic acid-[1 \rightarrow 3]-N-acetyl- β -galactosamine-4-sulfate-[1 \rightarrow 4]), or chondroitin sulfate C (an alternating copolymer of β -glucuronic acid-[1 \rightarrow 3]-N-acetyl- β -galactosamine-6-sulfate-[1 \rightarrow 4]), or a mixture thereof. 25 Chondroitin sulfate that is used in the present method and compositions should be of pharmaceutically acceptable quality.

30 The chondroitin sulfate can be supplied in a purified form, or by fractions, hydrolyzates, isolates, or extracts of cartilage or other natural materials, which fractions, hydrolyzates, isolates or extracts contain either chondroitin sulfate A, or chondroitin sulfate C, or a mixture of these two. Common methods of producing chondroitin sulfate involve purification from bovine, whale and shark cartilage. The chondroitin sulfate can be in

the form of a salt and, particularly when supplied as an isolate from a naturally occurring material, can be accompanied by other naturally occurring materials, as long as they are also pharmaceutically acceptable.

5 It is believed that chondroitin sulfate having a lower relative molecular weight is better absorbed orally than products having higher molecular weight. A preferred chondroitin sulfate has a weight average molecular weight of less than about 16.9 kilodaltons, and a molecular weight of less than about 10 kilodaltons is more preferred.

10 A preferred type of chondroitin sulfate A is that supplied as Product Number C-8529, by Sigma Chemical Co., St. Louis, MO. A preferred type of chondroitin sulfate C is that supplied as Product Number C-4384, by Sigma Chemical Co., St. Louis, MO. Moreover, the chondroitin sulfate can be supplied as any one or more of the chondroitin disaccharides listed as Product Numbers C-3920, C-4045, C-4170, C-5820, C-3670, C-5445, C-15 5320, and C-5945, in the Sigma Catalog, 2000 - 2001, Sigma Chemical Co., St. Louis, MO.

20 The chondroitin sulfate of the present method is administered with a cyclooxygenase-2 selective inhibitor. Any cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof that meets the criteria described below can be used in the subject method.

25 Another component of the combination of the present invention is a cyclooxygenase-2 selective inhibitor. The terms "cyclooxygenase-2 selective inhibitor", or "Cox-2 selective inhibitor", which can be used interchangeably herein, embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, and also include pharmaceutically acceptable salts of those compounds.

30 In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC₅₀ value for inhibition of Cox-1, divided by the IC₅₀ value for inhibition of Cox-2 (Cox-1 IC₅₀/Cox-2 IC₅₀). A Cox-2 selective inhibitor is

any inhibitor for which the ratio of Cox-1 IC₅₀ to Cox-2 IC₅₀ is greater than

1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

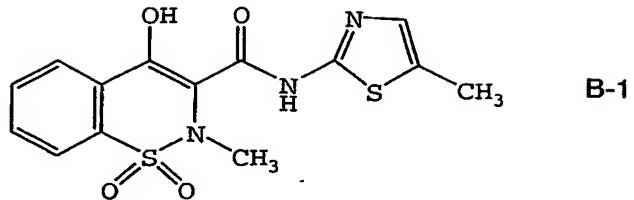
5 As used herein, the term "IC₅₀" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred cyclooxygenase-2 selective inhibitors of the present invention have a cyclooxygenase-2 IC₅₀ of less than about 1 μ M, more preferred of less than about 0.5 μ M, and even more preferred of less than 10 about 0.2 μ M.

Preferred cyclooxygenase-2 selective inhibitors have a cyclooxygenase-1 IC₅₀ of greater than about 1 μ M, and more preferably of greater than 20 μ M. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

15 Also included within the scope of the present invention are compounds that act as prodrugs of cyclooxygenase-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes 20 within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is parecoxib sodium. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent 25 No. 5,932,598.

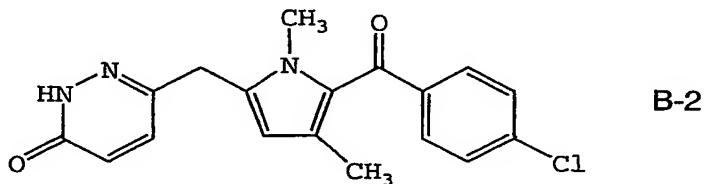
The cyclooxygenase-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.

30



5 In another embodiment of the invention the cyclooxygenase-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[(5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl)methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.

10



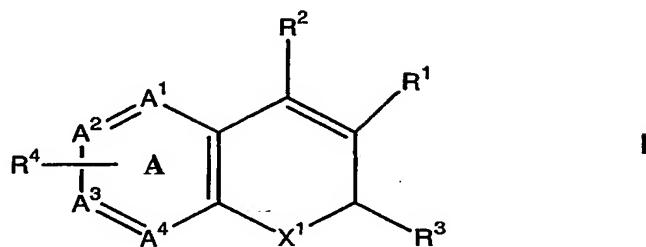
15

20

In another embodiment of the invention the cyclooxygenase-2 selective inhibitor is of the chromene/chroman structural class that is a substituted benzopyran or a substituted benzopyran analog, and even more preferably selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the compounds having a structure shown by general Formulas I, II, III, IV, V, and VI, shown below, and possessing, by way of example and not limitation, the structures disclosed in Table 1, including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

Benzopyrans that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent No. 6,271,253. One such

class of compounds is defined by the general formula shown below in formulas I:



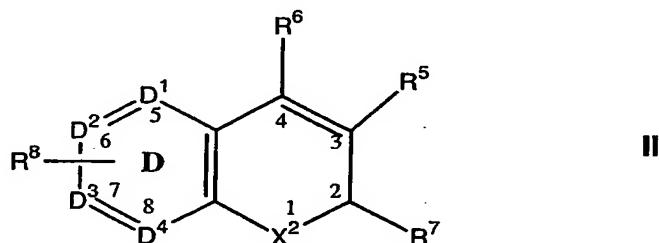
5 wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a ;
 wherein R^a is selected from hydrido, $C_1 - C_3$ -alkyl, (optionally substituted phenyl)- $C_1 - C_3$ -alkyl, acyl and carboxy- $C_1 - C_6$ -alkyl;
 wherein each of R^b and R^c is independently selected from hydrido,
 $C_1 - C_3$ -alkyl, phenyl- $C_1 - C_3$ -alkyl, $C_1 - C_3$ -perfluoroalkyl, chloro, $C_1 - C_6$ -alkylthio, $C_1 - C_6$ -alkoxy, nitro, cyano and cyano- $C_1 - C_3$ -alkyl; or wherein
 10 $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;
 wherein R^1 is selected from carboxyl, aminocarbonyl, $C_1 - C_6$ -alkylsulfonylaminocarbonyl and $C_1 - C_6$ -alkoxycarbonyl;
 wherein R^2 is selected from hydrido, phenyl, thienyl, $C_1 - C_6$ -alkyl and $C_2 - C_6$ -alkenyl;
 15 wherein R^3 is selected from $C_1 - C_3$ -perfluoroalkyl, chloro, $C_1 - C_6$ -alkylthio, $C_1 - C_6$ -alkoxy, nitro, cyano and cyano- $C_1 - C_3$ -alkyl;
 wherein R^4 is one or more radicals independently selected from
 hydrido, halo, $C_1 - C_6$ -alkyl, $C_2 - C_6$ -alkenyl, $C_2 - C_6$ -alkynyl, halo- $C_2 - C_6$ -alkynyl, aryl- $C_1 - C_3$ -alkyl, aryl- $C_2 - C_6$ -alkynyl, aryl- $C_2 - C_6$ -alkenyl, $C_1 - C_6$ -alkoxy, methylenedioxy, $C_1 - C_6$ -alkylthio, $C_1 - C_6$ -alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, $C_1 - C_6$ -alkoxy- $C_1 - C_6$ -alkyl, aryl- $C_1 - C_6$ -alkyloxy, heteroaryl- $C_1 - C_6$ -alkyloxy, aryl- $C_1 - C_6$ -alkoxy- $C_1 - C_6$ -alkyl, $C_1 - C_6$ -haloalkyl, $C_1 - C_6$ -haloalkoxy, $C_1 - C_6$ -haloalkylthio, $C_1 - C_6$ -haloalkylsulfinyl, $C_1 - C_6$ -(haloalkyl- $C_1 - C_3$ -

hydroxyalkyl, $C_1 - C_6$ -hydroxyalkyl, hydroxyimino- $C_1 - C_6$ -alkyl, $C_1 - C_6$ -alkylamino, arylamino, aryl- $C_1 - C_6$ -alkylamino, heteroarylarnino, heteroaryl- $C_1 - C_6$ -alkylamino, nitro, cyano, amino, aminosulfonyl, $C_1 - C_6$ -alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl- $C_1 - C_6$ -alkylaminosulfonyl, heteroaryl- $C_1 - C_6$ -alkylaminosulfonyl, heterocyclsulfonyl, $C_1 - C_6$ -alkylsulfonyl, aryl- $C_1 - C_6$ -alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl- $C_1 - C_6$ -alkylcarbonyl, heteroaryl- $C_1 - C_6$ -alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, $C_1 - C_6$ -alkoxycarbonyl, formyl, $C_1 - C_6$ -haloalkylcarbonyl and $C_1 - C_6$ -alkylcarbonyl; and

wherein the A ring atoms A^1 , A^2 , A^3 and A^4 are independently selected from carbon and nitrogen with the proviso that at least two of A^1 , A^2 , A^3 and A^4 are carbon;

or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxaliny and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes a compound having the structure of formula III:



20

wherein X^2 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, $C_1 - C_3$ -alkyl, (optionally substituted phenyl)- $C_1 - C_3$ -alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy- $C_1 - C_6$ -alkyl;

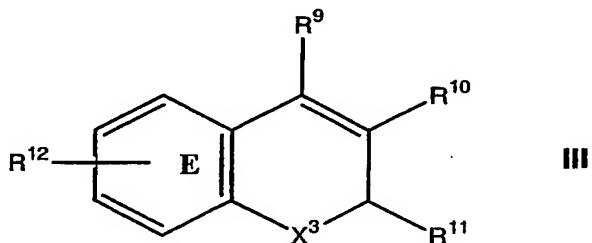
wherein each of R^b and R^c is independently selected from hydrido, C_1 - C_3 - alkyl, phenyl- C_1 - C_3 - alkyl, C_1 - C_3 - perfluoroalkyl, chloro, C_1 - C_6 - alkylthio, C_1 - C_6 - alkoxy, nitro, cyano and cyano- C_1 - C_3 - alkyl; or wherein $CR^c R^b$ form a cyclopropyl ring;

- 5 wherein R^5 is selected from carboxyl, aminocarbonyl, C_1 - C_6 - alkylsulfonylaminocarbonyl and C_1 - C_6 - alkoxycarbonyl; wherein R^6 is selected from hydrido, phenyl, thienyl, C_2 - C_6 - alkynyl and C_2 - C_6 - alkenyl; wherein R^7 is selected from C_1 - C_3 - perfluoroalkyl, chloro, C_1 - C_6 - alkylthio, C_1 - C_6 - alkoxy, nitro, cyano and cyano- C_1 - C_3 - alkyl; 10 wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1 - C_6 - alkyl, C_2 - C_6 - alkenyl, C_2 - C_6 - alkynyl, halo- C_2 - C_6 - alkynyl, aryl- C_1 - C_3 - alkyl, aryl- C_2 - C_6 - alkynyl, aryl- C_2 - C_6 - alkenyl, C_1 - C_6 - alkoxy, methylenedioxy, C_1 - C_6 - alkylthio, C_1 - C_6 - alkylsulfinyl, $—O(CF_2)_2 O—$, 15 aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 - C_6 - alkoxy- C_1 - C_6 - alkyl, aryl- C_1 - C_6 - alkyloxy, heteroaryl- C_1 - C_6 - alkyloxy, aryl- C_1 - C_6 - alkoxy- C_1 - C_6 - alkyl, C_1 - C_6 - haloalkyl, C_1 - C_6 - haloalkoxy, C_1 - C_6 - haloalkylthio, C_1 - C_6 - haloalkylsulfinyl, C_1 - C_6 - haloalkylsulfonyl, C_1 - C_3 - (haloalkyl- C_1 - C_3 - hydroxyalkyl), C_1 - C_6 - hydroxyalkyl, hydroxyimino- C_1 - C_6 - alkyl, C_1 - C_6 - alkylamino, arylamino, aryl- C_1 - C_6 - alkylamino, heteroarylamino, 20 heteroaryl- C_1 - C_6 - alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 - C_6 - alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl- C_1 - C_6 - alkylaminosulfonyl, heteroaryl- C_1 - C_6 - alkylaminosulfonyl, heterocyclsulfonyl, C_1 - C_6 - alkylsulfonyl, aryl- C_1 - C_6 - alkylsulfonyl, 25 optionally substituted aryl, optionally substituted heteroaryl, aryl- C_1 - C_6 - alkylcarbonyl, heteroaryl- C_1 - C_6 - alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 - C_6 - alkoxycarbonyl, formyl, C_1 - C_6 - haloalkylcarbonyl and C_1 - C_6 - alkylcarbonyl; and wherein the D ring atoms D^1 , D^2 , D^3 and D^4 are independently selected from carbon and nitrogen with the proviso that at least two of D^1 , D^2 , D^3 and D^4 are carbon; or

wherein R⁸ together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

Other benzopyran Cox-2 selective inhibitors useful in the practice of
5 the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula III:

Formula III is:



10

wherein X³ is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

wherein R⁹ is selected from the group consisting of H and aryl;

wherein R¹⁰ is selected from the group consisting of carboxyl,

15 aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxy carbonyl;

wherein R¹¹ is selected from the group consisting of haloalkyl, alkyl,

aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R¹² is selected from the group consisting of one or more

20 radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy,

heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy,

alkylamino, arylamino, aralkylamino, heteroaryl amino,

heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl,

arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl,

25 heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl,

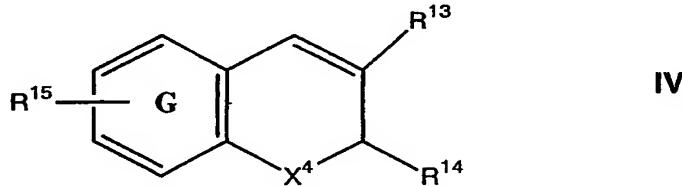
hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally

substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or

wherein R¹² together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and

5 including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

A related class of compounds useful as cyclooxygenase-2 selective inhibitors in the present invention is described by Formulas IV and V:



10

wherein X⁴ is selected from O or S or NR^a;

wherein R^a is alkyl;

wherein R¹³ is selected from carboxyl, aminocarbonyl,

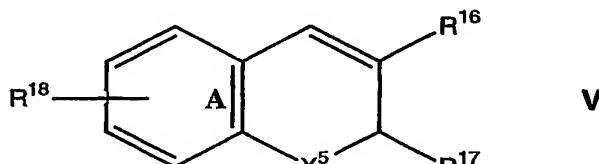
15 alkylsulfonylaminocarbonyl and alkoxy carbonyl;

wherein R¹⁴ is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

20 wherein R¹⁵ is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R¹⁵ together with ring G forms a naphthyl radical;
or an isomer or pharmaceutically acceptable salt thereof.

Formula V is:



5

wherein:

X⁵ is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

10 R¹⁶ is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxy carbonyl;
R¹⁷ is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and
15 R¹⁸ is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkyloxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R¹⁸ together with ring A forms a naphthyl radical;

20 or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;

5 R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered

10 heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

 wherein R^{18} together with ring A forms a naphthyl radical;

15 or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

20 R^{17} is lower haloalkyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl,

25 lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

 or an isomer or pharmaceutically acceptable salt thereof.

30 The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;

R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropoxy, *tert*butyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R^2 together with ring A forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;

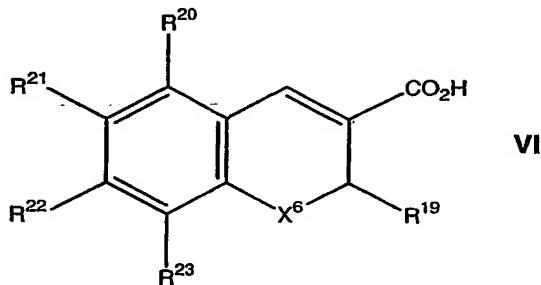
R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl,

benzylcarbonyl, and phenyl; or wherein R¹⁸ together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

5 The cyclooxygenase-2 selective inhibitor of the present invention can also be a compound having the structure of Formula VI:



wherein:

X⁶ is selected from the group consisting of O and S;

10 R¹⁹ is lower haloalkyl;

R²⁰ is selected from the group consisting of hydrido, and halo;

15 R²¹ is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

20 R²² is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

25 R²³ is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

The cyclooxygenase-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

25 X⁶ is selected from the group consisting of O and S;

R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

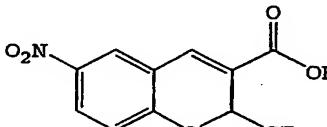
5 R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

10 R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

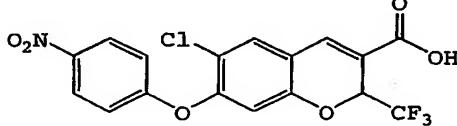
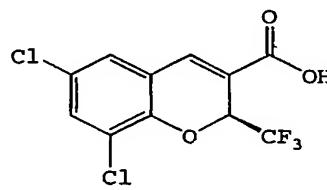
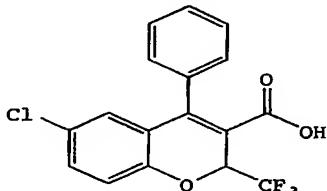
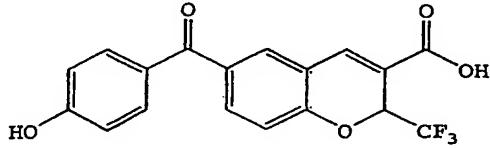
R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;
or an isomer or prodrug thereof.

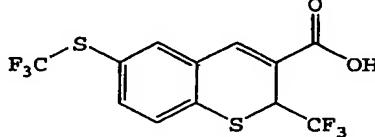
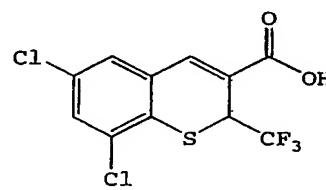
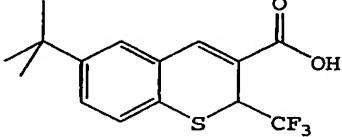
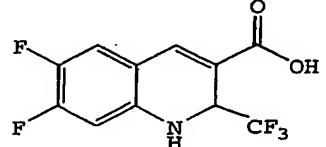
15

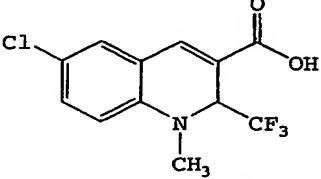
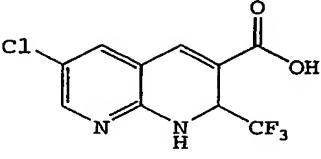
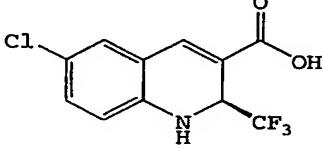
Table 1. Examples of Chromene Cox-2 Selective Inhibitors

| <u>Compound Number</u> | <u>Structural Formula</u> |
|------------------------|---|
| B-3 |  <p>6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid</p> |

| <u>Compound Number</u> | <u>Structural Formula</u> |
|----------------------------|---|
| B-4 | <p>6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid</p> |
| B-5 | <p>(S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p> |
| B-6 | <p>2-Trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid</p> |

| <u>Compound Number</u> | <u>Structural Formula</u> |
|----------------------------|---|
| B-7 |  <p>6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p> |
| B-8 |  <p>(S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p> |
| B-9 |  <p>6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid</p> |
| B-10 |  <p>6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid</p> |

| <u>Compound</u> <u>Number</u> | <u>Structural Formula</u> |
|----------------------------------|---|
| B-11 |  <p>2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid</p> |
| B-12 |  <p>6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid</p> |
| B-13 |  <p>6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid</p> |
| B-14 |  <p>6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid</p> |

| <u>Compound Number</u> | <u>Structural Formula</u> |
|----------------------------|---|
| B-15 |  <p>6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid</p> |
| B-16 |  <p>6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid</p> |
| B-17 |  <p>(S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid</p> |

Examples of specific compounds that are useful for the cyclooxygenase-2 selective inhibitor include (without limitation):

- 5 a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;
- a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

- a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;
- a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;
- 5 a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
- a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;
- 10 a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- 15 b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide
- b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 20 b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 25 b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 30 b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

- c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5 c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- 10 c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 15 c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;
- d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 20 d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- 25 d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- 30 d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

- d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
- e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-
- 5 benzylaminothiazole;
- e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
- e4) 2-[(3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;
- 10 e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;
- e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-
- 15 yl]benzenesulfonamide;
- e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
- e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-
- yl]benzenesulfonamide;
- 20 e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
- f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
- f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-
- 25 carbonitrile;
- f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 30 f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

- f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- f7) 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 5 f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 10 g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 15 g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
- g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
- g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- 20 g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
- 25 g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 30 h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

- h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 5 h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 10 h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- h10) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;
- 15 i1) N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
- i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
- 20 i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
- i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
- i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- 25 i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;
- i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
- 30 i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

- i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyoxy)-6-(trifluoromethyl)pyridine;
- 5 j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
- j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;
- 10 j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;
- j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
- j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
- 15 j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 20 k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 25 k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
- k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 30 k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

- k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
5 l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
10 l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzyl-acetate;
15 l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;
l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
20 and
m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.
m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic
25 acid;
m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
30 m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

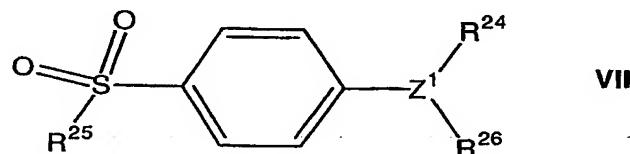
- m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;
- 25 o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p4) 6-[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 q1) 8-chloro-6-[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q5) 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;
- r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;
- r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 15 r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
- 20 r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
- r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 25 r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
- s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or
- 30 s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;
- or a pharmaceutically acceptable salt or prodrug thereof.

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of formula VII:

5



wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocycl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocycl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

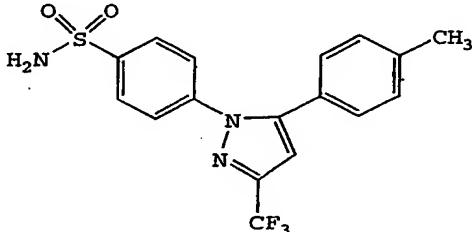
R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycl, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocycl, cycloalkenyl, aralkyl, heterocyclalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl- N- arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N- arylamino, N- aralkylamino, N-alkyl- N- aralkylamino, N-alkyl- N- arylamino, aminoalkyl, alkylaminoalkyl, N- arylaminoalkyl, N- aralkylaminoalkyl, N-alkyl-

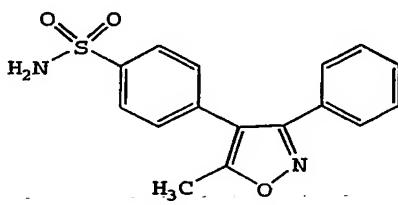
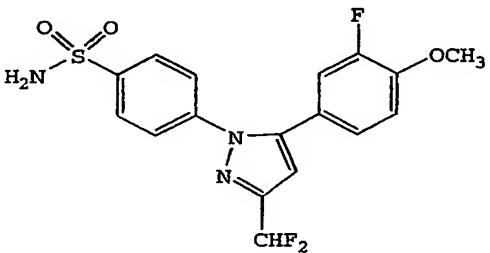
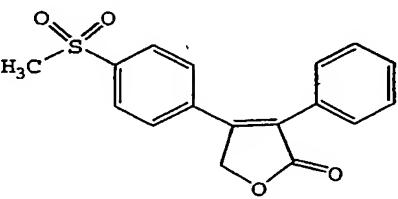
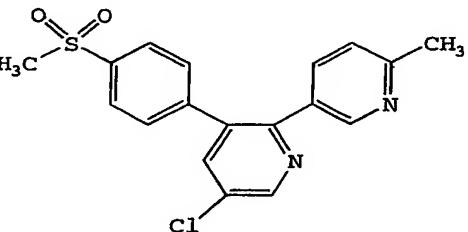
N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminoalkyl, arylsulfonyl, N-alkyl-N-arylaminoalkyl; or a prodrug thereof.

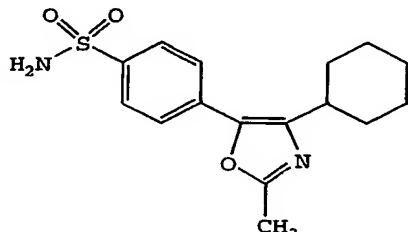
5 In a preferred embodiment of the invention the cyclooxygenase-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-18), valdecoxib (B-19), deracoxib (B-20), rofecoxib (B-21), etoricoxib (MK-663; B-22), JTE-522 (B-23), or a prodrug thereof.

10 Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-15 26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

Table 2. Examples of Tricyclic COX-2 Selective Inhibitors

| <u>Compound Number</u> | <u>Structural Formula</u> |
|------------------------|--|
| B-18 |  |

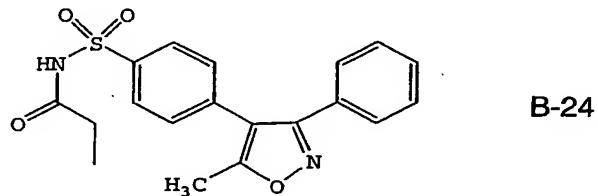
| <u>Compound Number</u> | <u>Structural Formula</u> |
|----------------------------|--|
| B-19 |  |
| B-20 |  |
| B-21 |  |
| B-22 |  |

| <u>Compound Number</u> | <u>Structural Formula</u> |
|------------------------|--|
| B-23 |  |

In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

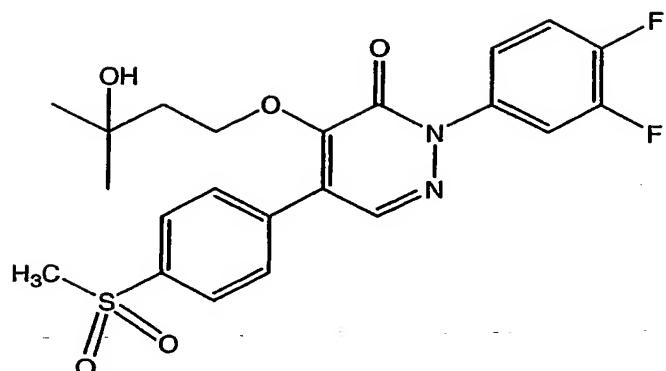
5 In a preferred embodiment of the invention, parecoxib (See, e.g. U.S. Patent No. 5,932,598), having the structure shown in B-24, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, (See, e.g., U.S. Patent No. 5,633,272), may be advantageously employed as a source of a cyclooxygenase inhibitor.

10



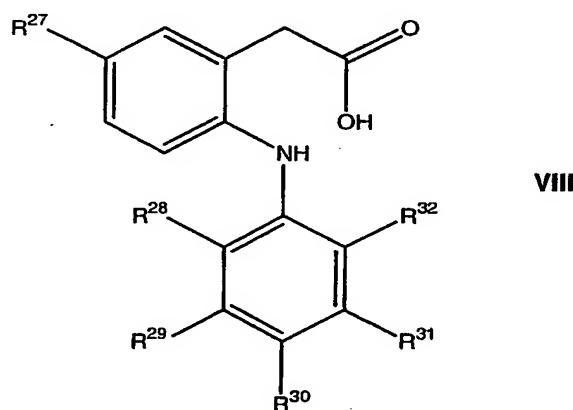
A preferred form of parecoxib is sodium parecoxib.

15 In another embodiment of the invention, the compound ABT-963 having the formula B-25 that has been previously described in International Publication number WO 00/24719, is another tricyclic cyclooxygenase-2 selective inhibitor which may be advantageously employed.



B-25

5 In a further embodiment of the invention, the cyclooxygenase inhibitor can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula **VIII**:



10

wherein:

R²⁷ is methyl, ethyl, or propyl;

R^{28} is chloro or fluoro;

R²⁹ is hydrogen, fluoro, or methyl;

15 R³⁰ is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R^{28} , R^{29} , R^{30} and R^{31} are not all fluoro when R^{27} is ethyl and R^{30} is H.

5 A phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in Formula VIII,

wherein:

R^{27} is ethyl;

10 R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor is a compound that has the structure shown in Formula VIII,

15 wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

20 Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib), having CAS Reg. No. 220991-20-8, and having the structure shown in Formula VIII,

wherein:

25 R^{27} is methyl;

R^{28} is fluoro;

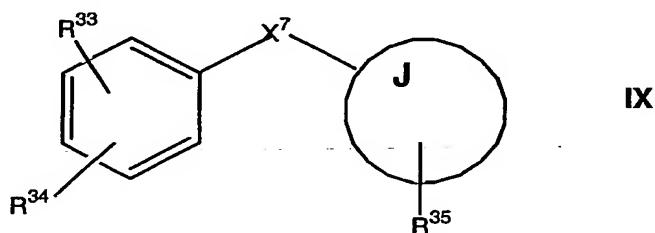
R^{32} is chloro; and

R^{29} , R^{30} , and R^{31} are hydrogen.

30 Compounds that have a structure similar to that shown in Formula VIII, which can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,310,099, 6,291,523, and 5,958,978.

Other cyclooxygenase-2 selective inhibitors that can be used in the present invention have the general structure shown in formula IX, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:

5



wherein:

X is O; J is 1-phenyl; R³³ is 2-NHSO₂CH₃; R³⁴ is 4-NO₂; and there is 10 no R³⁵ group, (nimesulide), and

X is O; J is 1-oxo-inden-5-yl; R³³ is 2-F; R³⁴ is 4-F; and R³⁵ is 6-NHSO₂CH₃, (flosulide); and

X is O; J is cyclohexyl; R³³ is 2-NHSO₂CH₃; R³⁴ is 5-NO₂; and there is no R³⁵ group, (NS-398); and

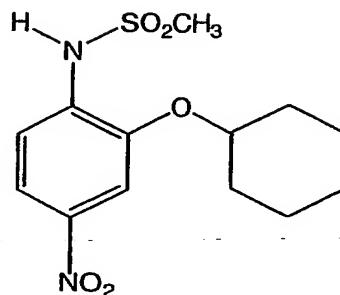
15 X is S; J is 1-oxo-inden-5-yl; R³³ is 2-F; R³⁴ is 4-F; and R³⁵ is 6-N⁻SO₂CH₃ · Na⁺, (L-745337); and

X is S; J is thiophen-2-yl; R³³ is 4-F; there is no R³⁴ group; and R³⁵ is 5-NHSO₂CH₃, (RWJ-63556); and

20 X is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R³³ is 3-F; R³⁴ is 4-F; and R³⁵ is 4-(p-SO₂CH₃)C₆H₄, (L-784512).

Further information on the applications of the Cox-2 selective inhibitor N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (NS-398, CAS RN 123653-11-2), having a structure as shown in formula B-26, have been described by, for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res.*, 90(4):406 - 412 (1999); Falgueyret, J.-P. *et al.*, in *Science Spectra*, 25 available at: http://www.gbhap.com/Science_Spectra/20-1-article.htm

(06/06/2001); and Iwata, K. *et al.*, in *Jpn. J. Pharmacol.*, 75(2):191 - 194 (1997).

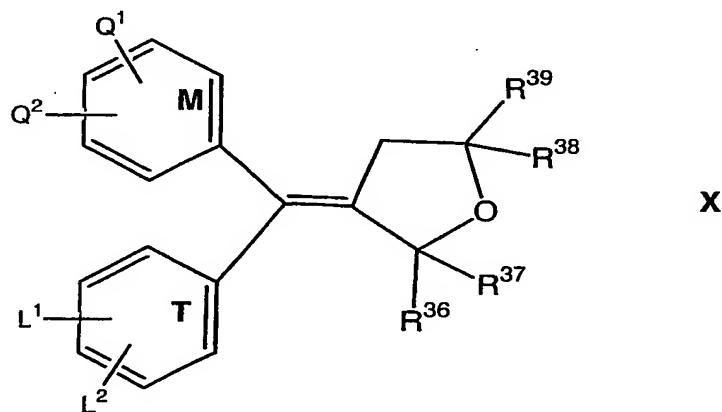


B-26

5

An evaluation of the anti-inflammatory activity of the cyclooxygenase-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther* 282, 1094-1101 (1997).

10 Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula X:



15

wherein:

the rings T and M independently are:
a phenyl radical,

a naphthyl radical,
a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or
a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

5 at least one of the substituents Q¹, Q², L¹ or L² is:
an —S(O)_n —R group, in which n is an integer equal to 0, 1 or 2 and R is:
a lower alkyl radical having 1 to 6 carbon atoms or
a lower haloalkyl radical having 1 to 6 carbon atoms, or
10 an -SO₂NH₂ group;
and is located in the para position,
the others independently being:
a hydrogen atom,
a halogen atom,
15 a lower alkyl radical having 1 to 6 carbon atoms,
a trifluoromethyl radical, or
a lower O-alkyl radical having 1 to 6 carbon atoms, or
Q¹ and Q² or L¹ and L² are a methylenedioxy group; and
R³⁶, R³⁷, R³⁸ and R³⁹ independently are:
20 a hydrogen atom,
a halogen atom,
a lower alkyl radical having 1 to 6 carbon atoms,
a lower haloalkyl radical having 1 to 6 carbon atoms, or
an aromatic radical selected from the group consisting of phenyl,
25 naphthyl, thienyl, furyl and pyridyl; or,
R³⁶, R³⁷ or R³⁸, R³⁹ are an oxygen atom, or
R³⁶, R³⁷ or R³⁸, R³⁹, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;
30 or an isomer or prodrug thereof.
Particular materials that are included in this family of compounds, and which can serve as the cyclooxygenase-2 selective inhibitor in the

present invention, include N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene)methyl]benzenesulfonamide.

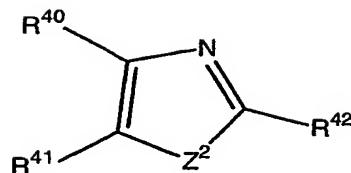
5 Cyclooxygenase-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

10 Information about S-33516, mentioned above, can be found in 15 *Current Drugs Headline News*, at <http://www.current-drugs.com/NEWS/Inflam1.htm>, 10/04/2001, where it was reported that S-33516 is a tetrahydroisoindole derivative which has IC₅₀ values of 0.1 and 0.001 mM against cyclooxygenase-1 and cyclooxygenase-2, respectively. In human whole blood, S-33516 was reported to have an ED₅₀ = 0.39 20 mg/kg.

25 Compounds that may act as cyclooxygenase-2 selective inhibitors include multibinding compounds containing from 2 to 10 ligands covariantly attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

Compounds that may act as cyclooxygenase-2 inhibitors include conjugated linoleic acid that is described in U.S. Patent No. 6,077,868.

30 Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such heterocyclic aromatic oxazole compounds have the formula shown below in formula XI:

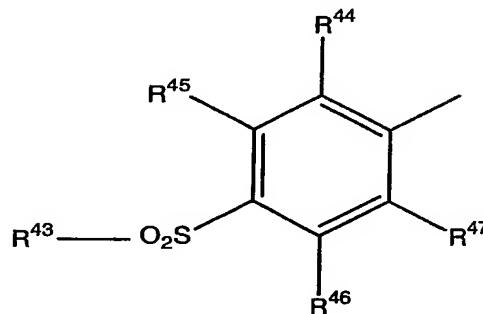


XI

wherein:

5 Z² is an oxygen atom;

one of R⁴⁰ and R⁴¹ is a group of the formula



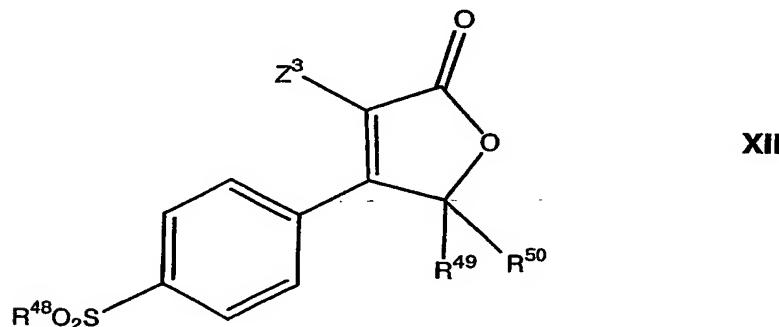
wherein:

10 R⁴³ is lower alkyl, amino or lower alkylamino; and

R⁴⁴, R⁴⁵, R⁴⁶ and R⁴⁷ are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy or amino, provided that at least one of R⁴⁴, R⁴⁵, R⁴⁶ and R⁴⁷ is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

15 R³⁰ is a lower alkyl or a halogenated lower alkyl, and a pharmaceutically acceptable salt thereof.

Cox-2 selective inhibitors that are useful in the subject method and compositions can include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by formula **XII**:



5

wherein:

Z^3 is selected from the group consisting of:

- (a) linear or branched C_{1-6} alkyl,
- 10 (b) linear or branched C_{1-6} alkoxy,
- (c) unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl

wherein the substituents are selected from the group consisting of:

- (1) hydrogen,
- (2) halo,
- 15 (3) C_{1-3} alkoxy,
- (4) CN,
- (5) C_{1-3} fluoroalkyl
- (6) C_{1-3} alkyl,
- (7) $-CO_2 H$;

20 R^{48} is selected from the group consisting of NH_2 and CH_3 ,

R^{49} is selected from the group consisting of:

C_{1-6} alkyl unsubstituted or substituted with C_{3-6} cycloalkyl, and
 C_{3-6} cycloalkyl;

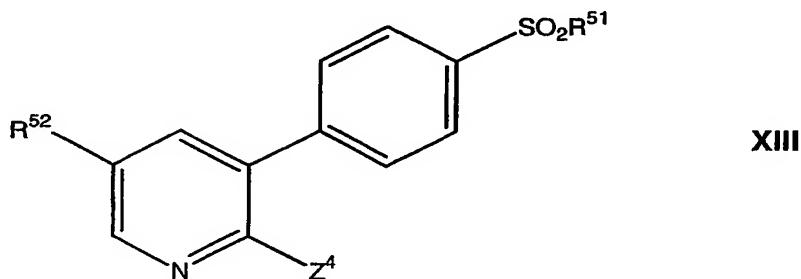
R^{50} is selected from the group consisting of:

C_{1-6} alkyl unsubstituted or substituted with one, two or three fluoro atoms; and

C_{3-6} cycloalkyl;

with the proviso that R^{49} and R^{50} are not the same.

5 Materials that can serve as cyclooxygenase-2 selective inhibitors include pyridines that are described in U.S. Patent Nos. 6,369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and which have the general formula described by formula XIII:



10

wherein:

R^{51} is selected from the group consisting of:

- (a) CH_3 ,
- (b) NH_2 ,
- (c) $NHC(O)CF_3$,
- (d) $NHCH_3$;

15 Z^4 is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof),

20 wherein the substituents are chosen from the group consisting of:

- (a) hydrogen,
- (b) halo,
- (c) C_{1-6} alkoxy,
- (d) C_{1-6} alkylthio,
- (e) CN ,

25

(f) C₁₋₆ alkyl,

(g) C₁₋₆ fluoroalkyl,

(h) N₃,

(i) —CO₂R⁵³,

5 (j) hydroxy,

(k) —C(R⁵⁴)(R⁵⁵)—OH,

(l) —C₁₋₆alkyl-CO₂—R⁵⁶,

(m) C₁₋₆fluoroalkoxy;

R⁵² is chosen from the group consisting of:

10 (a) halo,

(b) C₁₋₆alkoxy,

(c) C₁₋₆ alkylthio,

(d) CN,

(e) C₁₋₆ alkyl,

15 (f) C₁₋₆ fluoroalkyl,

(g) N₃,

(h) —CO₂R⁵⁷,

(i) hydroxy,

(j) —C(R⁵⁸)(R⁵⁹)—OH,

20 (k) —C₁₋₆alkyl-CO₂—R⁶⁰,

(l) C₁₋₆fluoroalkoxy,

(m) NO₂,

(n) NR⁶¹R⁶², and

(o) NHCOR⁶³;

25 R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶⁰, R⁶¹, R⁶², R⁶³, are each

independently chosen from the group consisting of:

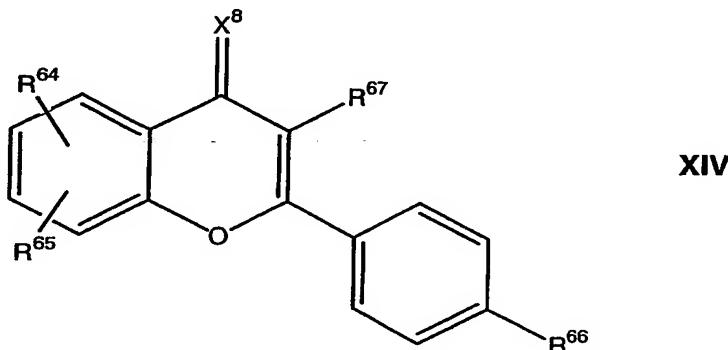
(a) hydrogen, and

(b) C₁₋₆alkyl;

30 or R⁵⁴ and R⁵⁵, R⁵⁸ and R⁵⁹ or R⁶¹ and R⁶² together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula XIV:

5



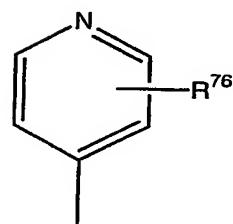
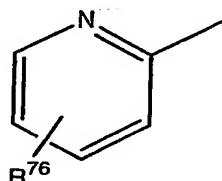
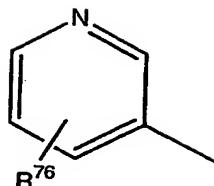
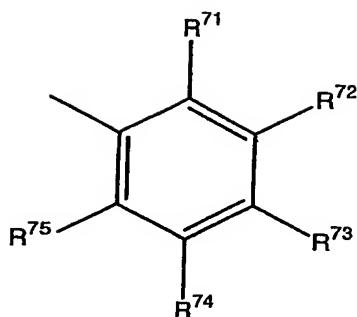
wherein:

X⁸ is an oxygen atom or a sulfur atom;

10 R⁶⁴ and R⁶⁵, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C₁-C₆ lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

15 R⁶⁶ is a group of a formula: S(O)_nR⁶⁸ wherein n is an integer of 0~2, R⁶⁸ is a hydrogen atom, a C₁-C₆ lower alkyl group, or a group of a formula: NR⁶⁹R⁷⁰ wherein R⁶⁹ and R⁷⁰, identical to or different from each other, are independently a hydrogen atom, or a C₁-C₆ lower alkyl group; and

20 R⁶⁷ is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C₁-C₆ lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:



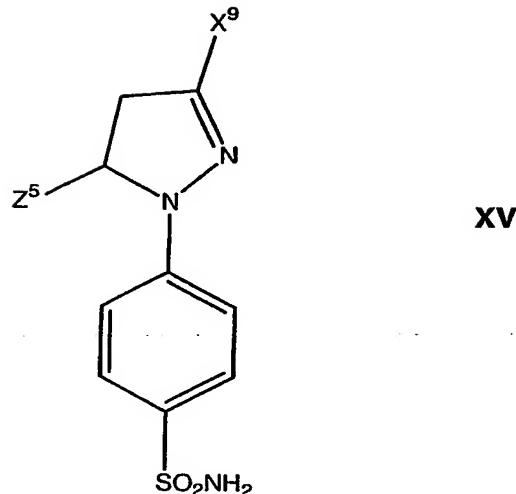
wherein:

5 R^{71} through R^{75} , identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: $NR^{69}R^{70}$, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,

10 wherein n , R^{68} , R^{69} and R^{70} have the same meaning as defined by R^{66} above; and

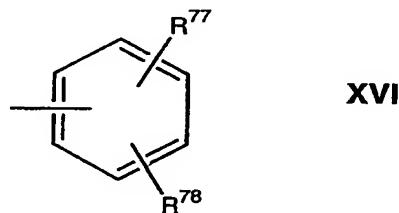
15 R^{76} is a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula XV:



wherein:

5 **X⁹** is selected from the group consisting of C₁ -C₆ trihalomethyl, preferably trifluoromethyl; C₁ -C₆ alkyl; and an optionally substituted or di-substituted phenyl group of formula **XVI**:



10

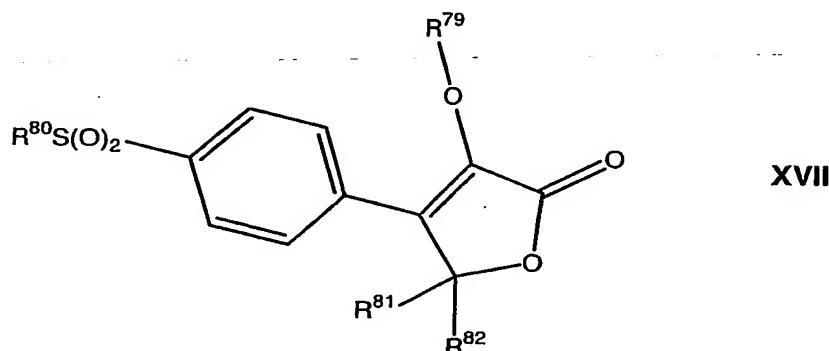
wherein:

15 R⁷⁷ and R⁷⁸ are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C₁ -C₆ alkyl, preferably C₁ -C₃ alkyl; C₁ -C₆ alkoxy, preferably C₁ -C₃ alkoxy; carboxy; C₁ -C₆ trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include heterocycles that are described in U.S.

5 Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



10 wherein:

R^{79} is a mono-, di-, or tri-substituted C_{1-12} alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_{2-10} alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_{2-10} alkynyl, or an unsubstituted or mono-, di- or tri-substituted

15 C_{3-12} cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted C_{5-12} cycloalkynyl, wherein the substituents are chosen from the group consisting of:

(a) halo, selected from F, Cl, Br, and I,

(b) OH,

(c) CF_3 ,

(d) C_{3-6} cycloalkyl,

(e) $=O$,

(f) dioxolane,

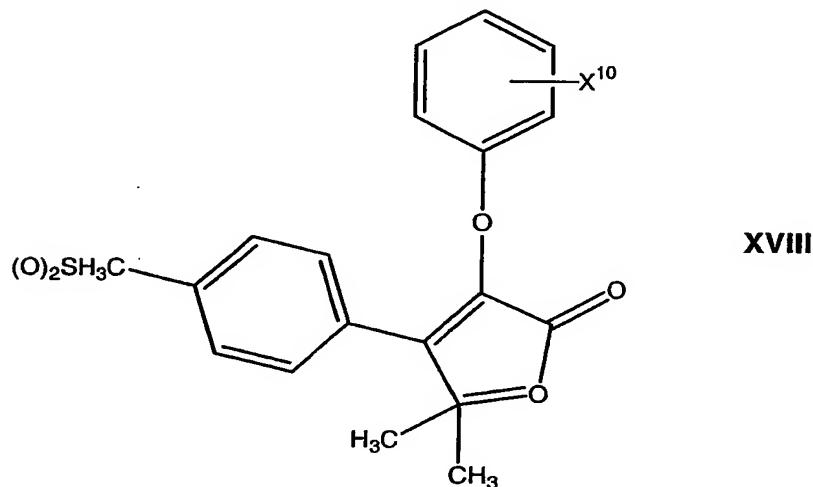
(g) CN; and

25 R^{80} is selected from the group consisting of:

- (a) CH_3 ,
- (b) NH_2 ,
- (c) NHC(O)CF_3 ,
- (d) NHCH_3 ;

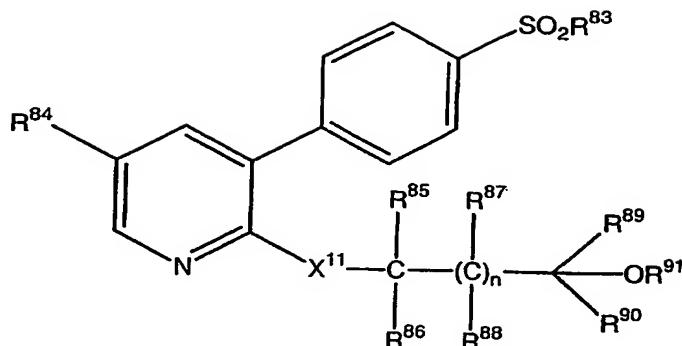
5 R^{81} and R^{82} are independently chosen from the group consisting of:
 (a) hydrogen,
 (b) C_{1-10} alkyl;
 or R^{81} and R^{82} together with the carbon to which they are attached
 form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

10 Formula XVIII is:



15 X^{10} is fluoro or chloro.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula XIX:



XIX

or a pharmaceutically acceptable salt thereof,
wherein:

- 5 X^{11} is selected from the group consisting of:
 (a) O,
 (b) S,
 (c) bond;
 n is 0 or 1;
- 10 R^{83} is selected from the group consisting of:
 (a) CH_3 ,
 (b) NH_2 ,
 (c) $NHC(O)CF_3$;
- 15 R^{84} is chosen from the group consisting of:
 (a) halo,
 (b) C_{1-6} alkoxy,
 (c) C_{1-6} alkylthio,
 (d) CN,
 (e) C_{1-6} alkyl,
 (f) C_{1-6} fluoroalkyl,
 (g) N_3 ,
 (h) $—CO_2 R^{92}$,
 (i) hydroxy,
 (j) $—C(R^{93})(R^{94})—OH$,
 (k) $—C_{1-6}$ alkyl- $CO_2 —R^{95}$,

(l) C₁₋₆ fluoroalkoxy,

(m) NO₂,

(n) NR⁹⁶ R⁹⁷,

(o) NHCOR⁹⁸;

5 R⁸⁵ to R⁹⁸ are independently chosen from the group consisting of

(a) hydrogen,

(b) C₁₋₆ alkyl;

or R⁸⁵ and R⁸⁹, or R⁸⁹ and R⁹⁰ together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R⁸⁵ and R⁸⁷ are joined to form a bond.

10 One preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is a bond.

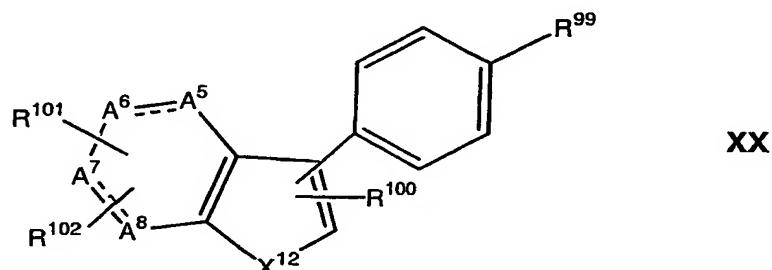
Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is O.

15 Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is S.

Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R⁸³ is CH₃.

20 Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R⁸⁴ is halo or C₁₋₆ fluoroalkyl.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula XX:



25

and pharmaceutically acceptable salts thereof wherein:

—A⁵=A⁶—A⁷=A⁸— is selected from the group consisting of:

- (a) —CH=CH—CH=CH—,
- (b) —CH₂—CH₂—CH₂—C(O)—, —CH₂—CH₂—C(O)—CH₂—,
- 5 —CH₂—C(O)—CH₂—CH₂, —C(O)—CH₂—CH₂—CH₂,
- (c) —CH₂—CH₂—C(O)—, —CH₂—C(O)—CH₂—, —C(O)—CH₂
- CH₂—
- (d) —CH₂—CH₂—O—C(O)—, CH₂—O—C(O)—CH₂—, —O—
- 10 C(O)—CH₂—CH₂—,
- (e) —CH₂—CH₂—C(O)—O—, —CH₂—C(O)—OCH₂—, —C(O)—
- O—CH₂—CH₂—,
- (f) —C(R¹⁰⁵)₂—O—C(O)—, —C(O)—O—C(R¹⁰⁵)₂—, —O—C(O)—
- C(R¹⁰⁵)₂—, —C(R¹⁰⁵)₂—C(O)—O—,
- (g) —N=CH—CH=CH—,
- 15 (h) —CH=N—CH=CH—,
- (i) —CH=CH—N=CH—,
- (j) —CH=CH—CH=N—,
- (k) —N=CH—CH=N—,
- (l) —N=CH—N=CH—,
- 20 (m) —CH=N—CH=N—,
- (n) —S—CH=N—,
- (o) —S—N=CH—,
- (p) —N=N—NH—,
- (q) —CH=N—S—, and
- 25 (r) —N=CH—S—;

R⁹⁹ is selected from the group consisting of:

- (a) S(O)₂ CH₃,
- (b) S(O)₂ NH₂,
- (c) S(O)₂ NHCOCF₃,
- 30 (d) S(O)(NH)CH₃,
- (e) S(O)(NH)NH₂,
- (f) S(O)(NH)NHCOCF₃,

(g) $\text{P}(\text{O})(\text{CH}_3)\text{OH}$, and

(h) $\text{P}(\text{O})(\text{CH}_3)\text{NH}_2$;

R^{100} is selected from the group consisting of:

5 (a) C_{1-6} alkyl,

(b) C_{3-7} , cycloalkyl,

(c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo, including F, Cl, Br, I,

10 (3) C_{1-6} alkoxy,

(4) C_{1-6} alkylthio,

(5) CN,

(6) CF_3 ,

(7) C_{1-6} alkyl,

15 (8) N_3 ,

(9) $-\text{CO}_2\text{H}$,

(10) $-\text{CO}_2-\text{C}_{1-4}$ alkyl,

(11) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{OH}$,

(12) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{O}-\text{C}_{1-4}$ alkyl, and

20 (13) $-\text{C}_{1-6}$ alkyl- $\text{CO}_2-\text{R}^{106}$;

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_{1-6} alkyl,

30 (4) C_{1-6} alkoxy,

(5) C_{1-6} alkylthio,

(6) CN,

- (7) CF_3 ,

(8) N_3 ,

(9) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{OH}$, and

(10) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{O}-\text{C}_{1-4}$ alkyl;

5 (e) benzoheteroaryl which includes the benzo fused analogs of (d). R^{101} and R^{102} are the substituents residing on any position of $-\text{A}^5=\text{A}^6-$ $\text{A}^7=\text{A}^8-$ and are selected independently from the group consisting of:

(a) hydrogen,

(b) CF_3 ,

10 (c) CN ,

(d) C_{1-6} alkyl,

(e) $-\text{Q}^3$ wherein Q^3 is Q^4 , CO_2H , $\text{C}(\text{R}^{103})(\text{R}^{104})\text{OH}$,

(f) $-\text{O}-\text{Q}^4$,

(g) $-\text{S}-\text{Q}^4$, and

15 (h) optionally substituted:

(1) $-\text{C}_{1-5}$ alkyl- Q^3 ,

(2) $-\text{O}-\text{C}_{1-5}$ alkyl- Q^3 ,

(3) $-\text{S}-\text{C}_{1-5}$ alkyl- Q^3 ,

(4) $-\text{C}_{1-3}$ alkyl- $\text{O}-\text{C}_{1-3}$ alkyl- Q^3 ,

20 (5) $-\text{C}_{1-3}$ alkyl- $\text{S}-\text{C}_{1-3}$ alkyl- Q^3 ,

(6) $-\text{C}_{1-5}$ alkyl- $\text{O}-\text{Q}^4$,

(7) $-\text{C}_{1-5}$ alkyl- $\text{S}-\text{Q}^4$,

wherein the substituent resides on the alkyl chain and the substituent is C_{1-3} alkyl, and Q^3 is Q^4 , CO_2H , $\text{C}(\text{R}^{103})(\text{R}^{104})\text{OH}$ Q^4 is CO_2 $-\text{C}_{1-4}$ alkyl, tetrazolyl-5-yl, or $\text{C}(\text{R}^{103})(\text{R}^{104})\text{O}-\text{C}_{1-4}$ alkyl;

25 R^{103} , R^{104} and R^{105} are each independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-6} alkyl; or

30 R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two

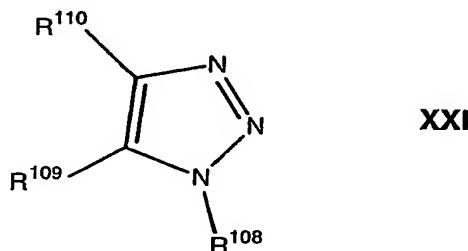
R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_{1-6} alkyl;

R^{107} is hydrogen, C_{1-6} alkyl or aryl;

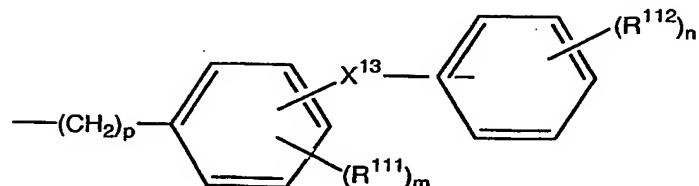
5 X^7 is O, S, NR^{107} , CO, $C(R^{107})_2$, $C(R^{107})(OH)$, $—C(R^{107})=C(R^{107})—$; $—C(R^{107})=N—$; $—N=C(R^{107})—$.

10 Compounds that may act as cyclooxygenase-2 inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula XXI:



wherein:

15 R^{108} is:

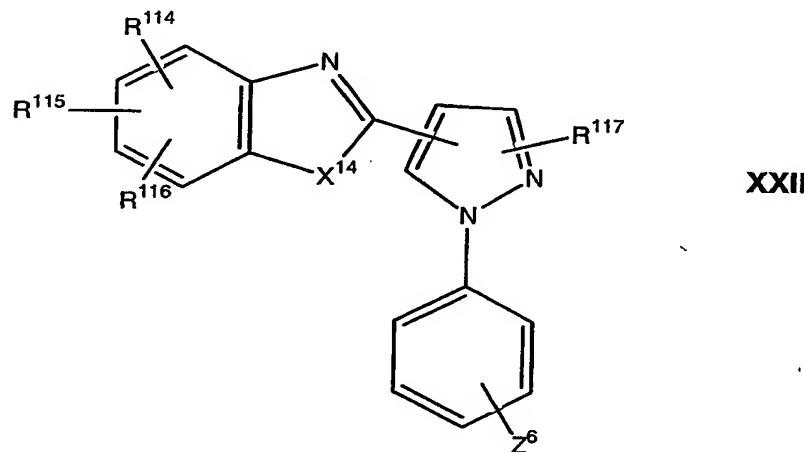


wherein:

20 p is 0 to 2; m is 0 to 4; and n is 0 to 5; X^{13} is O, S, SO , SO_2 , CO, $CHCN$, CH_2 or $C=NR^{113}$ where R^{113} is hydrogen, loweralkyl, hydroxy, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano; and, R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl,

loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifluoromethoxy, acetamido, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R¹⁰⁹ is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, formamido or guanidino; and R¹¹⁰ is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; wherein the loweralkyl, loweralkyl containing, loweralkoxy and loweralkanoyl groups contain from 1 to 3 carbon atoms.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyrazole derivatives that are described in U.S. Patent 6,136,831. Such pyrazole derivatives have the formula shown below in formula XXII:



15

wherein:

R¹¹⁴ is hydrogen or halogen, R¹¹⁵ and R¹¹⁶ are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or lower alkanoyloxy;

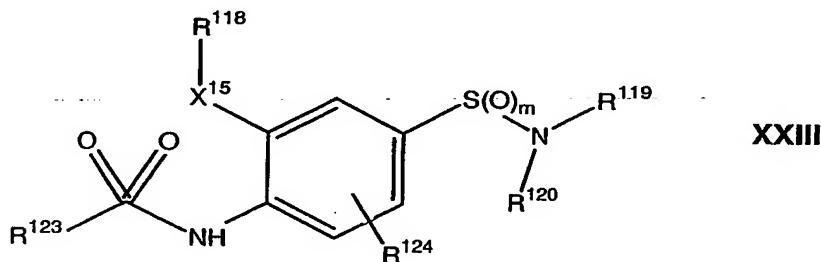
20 R¹¹⁷ is lower haloalkyl or lower alkyl;

X¹⁴ is sulfur, oxygen or NH; and

Z⁶ is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable salt thereof.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula 5 XXIII:



wherein:

- 10 X^{15} denotes oxygen, sulphur or NH;
 R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3 , 15 cyano or alkoxy;
- R^{119} and R^{120} , independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n-X^{16}$;
- R^{119} and R^{120} , together with the N- atom, denote a 3 to 7- 20 membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n-X^{16}$;
- X^{16} denotes halogen, NO_2 , $-OR^{121}$, $-COR^{121}$, $-CO_2R^{121}$, $-OCO_2R^{121}$, 25 $-CN$, $-CONR^{121}OR^{122}$, $-CONR^{121}R^{122}$, $-SR^{121}$, $-S(O)R^{121}$, $-S(O)_2R^{121}$, $-NR^{121}R^{122}$, $-NHC(O)R^{121}$, $-NHS(O)_2R^{121}$;
- n denotes a whole number from 0 to 6;

R^{123} denotes a straight-chained or branched alkyl group with 1-10 C-atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;

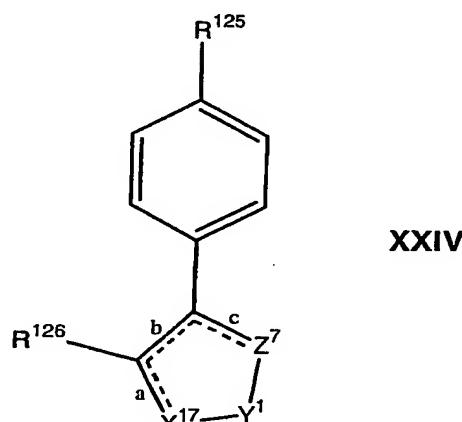
5 R^{124} denotes halogen, hydroxy, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C-atoms, which can optionally be mono- or polysubstituted by halogen, NO_2 , $-OR^{121}$, $-COR^{121}$, $-CO_2R^{121}$, $-OCO_2R^{121}$, $-CN$, $-CONR^{121}OR^{122}$, $-CONR^{122}R^{122}$, $-SR^{121}$, $-S(O)R^{121}$, $-S(O)_2R^{121}$, $-NR^{121}R^{122}$, $-NHC(O)R^{121}$, $-NHS(O)_2R^{121}$, or a polyfluoroalkyl group;

10 R^{121} and R^{122} , independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

m denotes a whole number from 0 to 2;

and the pharmaceutically-acceptable salts thereof.

15 Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 3-phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanones that are described in U.S. Patent 6,239,173. Such 3-phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanones have the formula shown below in formula XXIV:



20

or pharmaceutically acceptable salts thereof wherein:

X^{17} — Y^1 — Z^7 -is selected from the group consisting of:

- (a) —CH₂ CH₂ CH₂ —,
 - (b) —C(O)CH₂ CH₂ —,
 - 5 (c) —CH₂ CH₂ C(O)—,
 - (d) —CR¹²⁹ (R¹²⁹)—O—C(O)—,
 - (e) —C(O)—O—CR¹²⁹ (R¹²⁹)—,
 - (f) —CH₂—NR¹²⁷—CH₂—,
 - (g) —CR¹²⁹ (R¹²⁹)—NR¹²⁷—C(O)—,
 - 10 (h) —CR¹²⁸=CR¹²⁸—S—,
 - (i) —S—CR¹²⁸=CR¹²⁸—,
 - (j) —S—N=CH—,
 - (k) —CH=N—S—,
 - (l) —N=CR¹²⁸—O—,
 - 15 (m) —O—CR⁴=N— ,
 - (n) —N=CR¹²⁸—NH—,
 - (o) —N=CR¹²⁸—S—, and
 - (p) —S—CR¹²⁸=N—,
 - (q) —C(O)—NR¹²⁷—CR¹²⁹ (R¹²⁹)—,
 - 20 (r) —R¹²⁷ N—CH=CH— provided R₁₂₂ is not —S(O)₂CH₃,
 - (s) —CH=CH—NR¹²⁷— provided R¹²⁵ is not —S(O)₂CH₃,
 - when side b is a double bond, and sides a and c are single bonds;
 - and
- X^{17} — Y^1 — Z^7 -is selected from the group consisting of:
- (a) =CH—O—CH=, and
 - (b) =CH—NR¹²⁷—CH=,
 - (c) =N—S—CH=,
 - (d) =CH—S—N=,
 - (e) =N—O—CH=,
 - 25 (f) =CH—O—N=,
 - (g) =N—S—N=,
 - (h) =N—O—N=,

when sides a and c are double bonds and side b is a single bond;
R¹²⁵ is selected from the group consisting of:

(a) S(O)₂ CH₃,
(b) S(O)₂ NH₂,
5 (c) S(O)₂ NHC(O)CF₃,
(d) S(O)(NH)CH₃,
(e) S(O)(NH)NH₂,
(f) S(O)(NH)NHC(O)CF₃,
(g) P(O)(CH₃)OH, and
10 (h) P(O)(CH₃)NH₂;

R¹²⁶ is selected from the group consisting of

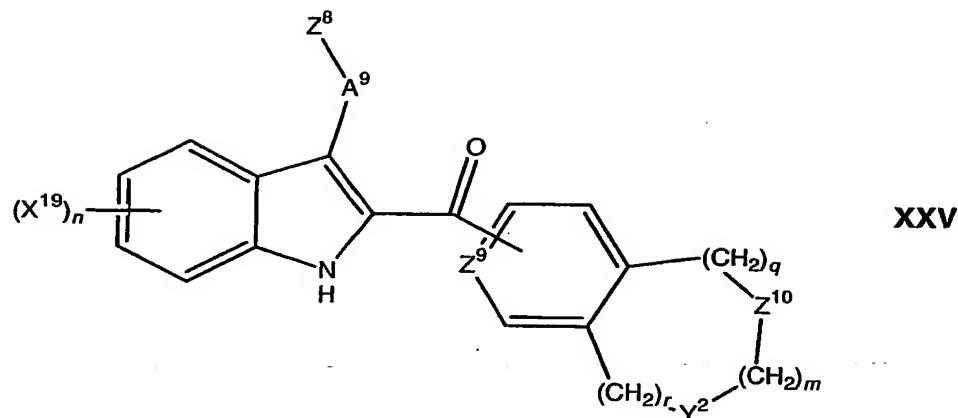
(a) C₁₋₆ alkyl,
(b) C₃, C₄, C₅, C₆, and C₇, cycloalkyl,
(c) mono-, di- or tri-substituted phenyl or naphthyl,
15 wherein the substituent is selected from the group consisting of:

(1) hydrogen,
(2) halo,
(3) C₁₋₆ alkoxy,
(4) C₁₋₆ alkylthio,
20 (5) CN,
(6) CF₃,
(7) C₁₋₆ alkyl,
(8) N₃,
(9) —CO₂ H,
25 (10) —CO₂ —C₁₋₄ alkyl,
(11) —C(R¹²⁹)(R¹³⁰)—OH,
(12) —C(R¹²⁹)(R¹³⁰)—O—C₁₋₄ alkyl, and
(13) —C₁₋₆ alkyl—CO₂ —R¹²⁹ ;
30 (d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero

atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

- (1) hydrogen,
- (2) halo, including fluoro, chloro, bromo and iodo,
- 5 (3) C₁₋₆ alkyl,
- (4) C₁₋₆ alkoxy,
- (5) C₁₋₆ alkylthio,
- (6) CN,
- (7) CF₃,
- 10 (8) N₃,
- (9) —C(R¹²⁹)(R¹³⁰)—OH, and
- (10) —C(R¹²⁹)(R¹³⁰)—O—C₁₋₄ alkyl;
- (e) benzoheteroaryl which includes the benzo fused analogs of (d); R¹²⁷ is selected from the group consisting of:
- 15 (a) hydrogen,
- (b) CF₃,
- (c) CN,
- (d) C₁₋₆ alkyl,
- (e) hydroxyC₁₋₆ alkyl,
- 20 (f) —C(O)—C₁₋₆ alkyl,
- (g) optionally substituted:
 - (1) —C₁₋₅ alkyl-Q⁵,
 - (2) —C₁₋₃ alkyl—O—C₁₋₃ alkyl-Q⁵,
 - (3) —C₁₋₃ alkyl—S—C₁₋₃ alkyl-Q⁵,
- 25 (4) —C₁₋₅ alkyl—O—Q⁵, or
- (5) —C₁₋₅ alkyl—S—Q⁵,
- wherein the substituent resides on the alkyl and the substituent is C₁₋₃ alkyl;
- (h) —Q⁵;
- 30 R¹²⁸ and R^{128'} are each independently selected from the group consisting of:

- (a) hydrogen,
 - (b) CF_3 ,
 - (c) CN,
 - (d) C_{1-6} alkyl,
 - 5 (e) $-\text{Q}^5$,
 - (f) $-\text{O}-\text{Q}^5$;
 - (g) $-\text{S}-\text{Q}^5$, and
 - (h) optionally substituted:
 - (1) $-\text{C}_{1-5}$ alkyl- Q^5 ,
 - 10 (2) $-\text{O}-\text{C}_{1-5}$ alkyl- Q^5 ,
 - (3) $-\text{S}-\text{C}_{1-5}$ alkyl- Q^5 ,
 - (4) $-\text{C}_{1-3}$ alkyl- $\text{O}-\text{C}_{1-3}$ alkyl- Q^5 ,
 - (5) $-\text{C}_{1-3}$ alkyl- $\text{S}-\text{C}_{1-3}$ alkyl- Q^5 ,
 - (6) $-\text{C}_{1-5}$ alkyl- $\text{O}-\text{Q}^5$,
 - 15 (7) $-\text{C}_{1-5}$ alkyl- $\text{S}-\text{Q}^5$,
- wherein the substituent resides on the alkyl and the substituent is C_{1-3} alkyl, and
- R^{129} , $\text{R}^{129'}$, R^{130} , R^{131} and R^{132} are each independently selected from the group consisting of:
- 20 (a) hydrogen,
 - (b) C_{1-6} alkyl;
 - or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;
- 25 Q^5 is CO_2H , $\text{CO}_2-\text{C}_{1-4}$ alkyl, tetrazolyl-5-yl, $\text{C}(\text{R}^{131})(\text{R}^{132})(\text{OH})$, or $\text{C}(\text{R}^{131})(\text{R}^{132})(\text{O}-\text{C}_{1-4}$ alkyl);
- provided that when $\text{X}-\text{Y}-\text{Z}$ is $-\text{S}-\text{CR}^{128}=\text{CR}^{128'}$, then R^{128} and $\text{R}^{128'}$ are other than CF_3 .
- Materials that can serve as a cyclooxygenase-2 selective inhibitor
- 30 of the present invention include bicycliccarbonyl indole compounds that are described in U.S. Patent No. 6,303,628. Such bicycliccarbonyl indole compounds have the formula shown below in formula XXV:

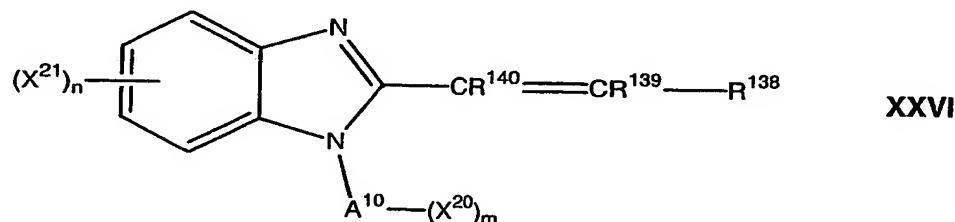


or the pharmaceutically acceptable salts thereof wherein

- 5 A^9 is C_{1-6} alkylene or $—NR^{133}—$;
- Z^8 is $C(=L^3)R^{134}$, or $SO_2 R^{135}$;
- Z^9 is CH or N;
- Z^{10} and Y^2 are independently selected from $—CH_2—$, O, S and $—N—R^{133}$;
- 10 m is 1, 2 or 3;
- q and r are independently 0, 1 or 2;
- X^{18} is independently selected from halogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, amino, mono- or di- $(C_{1-4}$ alkyl)amino and cyano;
- 15 n is 0, 1, 2, 3 or 4;
- L^3 is oxygen or sulfur;
- R^{133} is hydrogen or C_{1-4} alkyl;
- R^{134} is hydroxy, C_{1-6} alkyl, halo-substituted C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkoxy, C_{3-7} cycloalkoxy, C_{1-4} alkyl(C_{3-7} cycloalkoxy),
- 20 $—NR^{136} R^{137}$, C_{1-4} alkylphenyl-O— or phenyl-O—, said phenyl being optionally substituted with one to five substituents independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy and nitro;
- R^{135} is C_{1-6} alkyl or halo-substituted C_{1-6} alkyl; and

R^{136} and R^{137} are independently selected from hydrogen, C_{1-6} alkyl and halo-substituted C_{1-6} alkyl.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzimidazole compounds that are 5 described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula **XXVI**:



10 or a pharmaceutically acceptable salt thereof, wherein:

A^{10} is heteroaryl selected from a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

15 X^{20} is independently selected from halo, $C_1 - C_4$ alkyl, hydroxy, $C_1 - C_4$ alkoxy, halo-substituted $C_1 - C_4$ alkyl, hydroxy-substituted $C_1 - C_4$ alkyl, $(C_1 - C_4$ alkoxy) $C_1 - C_4$ alkyl, halo-substituted $C_1 - C_4$ alkoxy, amino, $N-(C_1 - C_4$ alkyl)amino, N, N -di($C_1 - C_4$ alkyl)amino, $[N-(C_1 - C_4$ alkyl)amino] $C_1 - C_4$ alkyl, $[N, N$ -di($C_1 - C_4$ alkyl)amino] $C_1 - C_4$ alkyl, $N-(C_1 - C_4$ alkanoyl)amino, $N-(C_1 - C_4$ alkyl)($C_1 - C_4$ alkanoyl)amino, $N-[(C_1 - C_4$ alkyl)sulfonyl]amino, $N-[(halo-substituted C_1 - C_4 alkyl)sulfonyl]amino$, $C_1 - C_4$ alkanoyl, carboxy, $(C_1 - C_4$ alkoxy)carbonyl, carbamoyl, $[N-(C_1 - C_4$ alkyl)amino]carbonyl, $[N, N$ -di($C_1 - C_4$ alkyl)amino]carbonyl, cyano, nitro, mercapto, $(C_1 - C_4$ alkyl)thio, $(C_1 - C_4$ alkyl)sulfinyl, $(C_1 - C_4$ alkyl)sulfonyl, aminosulfonyl, $[N-(C_1 - C_4$

alkyl)amino]sulfonyl and [N, N-di(C₁ -C₄ alkyl)amino]sulfonyl; X²¹ is independently selected from halo, C₁ -C₄ alkyl, hydroxy, C₁ -C₄ alkoxy, halo-substituted C₁ -C₄ alkyl, hydroxy-substituted C₁ -C₄ alkyl, (C₁ -C₄ alkoxy)C₁ -C₄ alkyl, halo-substituted C₁ -C₄ alkoxy, amino, N-(C₁ -C₄ alkyl)amino, N, N-di(C₁ -C₄ alkyl)amino, [N-(C₁ -C₄ alkyl)amino]C₁ -C₄ alkyl, [N, N-di(C₁ -C₄ alkyl)amino]C₁ -C₄ alkyl, N-(C₁ -C₄ alkanoyl)amino, N-(C₁ -C₄ alkyl)-N-(C₁ -C₄ alkanoyl) amino, N-[(C₁ -C₄ alkyl)sulfonyl]amino, N-[(halo-substituted C₁ -C₄ alkyl)sulfonyl]amino, C₁ -C₄ alkanoyl, carboxy, (C₁ -C₄ alkoxy)cabonyl, cabamoyl, [N-(C₁ -C₄ alkyl) amino]carbonyl, [N, N-di(C₁ -C₄ alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C₁ -C₄ alkyl)thio, (C₁ -C₄ alkyl)sulfinyl, (C₁ -C₄ alkyl)sulfonyl, aminosulfonyl, [N-(C₁ -C₄ alkyl)amino]sulfonyl and [N, N-di(C₁ -C₄ alkyl)amino]sulfonyl;

R¹³⁸ is selected from hydrogen,

15 straight or branched C₁ -C₄ alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo hydroxy, C₁ -C₄ alkoxy, amino, N-(C₁ -C₄ alkyl)amino and N, N-di(C₁ -C₄ alkyl)amino,

20 C₃ -C₈ cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C₁ -C₄ alkyl, hydroxy, C₁ -C₄ alkoxy, amino, N-(C₁ -C₄ alkyl)amino and N, N-di(C₁ -C₄ alkyl)amino,

25 C₄ -C₈ cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C₁ -C₄ alkyl, hydroxy, C₁ -C₄ alkoxy, amino, N-(C₁ -C₄ alkyl)amino and N, N-di(C₁ -C₄ alkyl)amino,

30 phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C₁ -C₄ alkyl, hydroxy, C₁ -C₄ alkoxy, halo-substituted C₁ -C₄ alkyl, hydroxy-substituted C₁ -C₄ alkyl, (C₁ -C₄ alkoxy)C₁ -C₄ alkyl, halo-substituted C₁ -C₄ alkoxy, amino, N-(C₁ -C₄ alkyl)amino, N, N-di(C₁ -C₄ alkyl)amino, [N-(C₁ -C₄ alkyl)amino]C₁ -C₄ alkyl, [N, N-di(C₁ -C₄ alkyl)amino]C₁ -C₄ alkyl, N-(C₁ -C₄ alkyl)amino, N, N-di(C₁ -C₄ alkyl)amino, [N-(C₁ -C₄ alkyl)amino]C₁ -C₄ alkyl, N-(C₁ -C₄ alkanoyl)amino, N-(C₁ -C₄ alkyl)-N-(C₁ -C₄ alkanoyl) amino, N-[(C₁ -C₄ alkyl)sulfonyl]amino, N-[(halo-substituted C₁ -C₄ alkyl)sulfonyl]amino, C₁ -C₄ alkanoyl, carboxy, (C₁ -C₄ alkoxy)cabonyl, cabamoyl, [N-(C₁ -C₄ alkyl) amino]carbonyl, [N, N-di(C₁ -C₄ alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C₁ -C₄ alkyl)thio, (C₁ -C₄ alkyl)sulfinyl, (C₁ -C₄ alkyl)sulfonyl, aminosulfonyl, [N-(C₁ -C₄ alkyl)amino]sulfonyl and [N, N-di(C₁ -C₄ alkyl)amino]sulfonyl;

-C₄ alkanoyl)amino, N-[C₁ -C₄ alkyl)(C₁ -C₄ alkanoyl)]amino, N-[(C₁ -C₄ alkyl)sulfonyl]amino, N-[(halo-substituted C₁ -C₄ alkyl)sulfonyl]amino, C₁ -C₄ alkanoyl, carboxy, (C₁ -C₄ alkoxy)carbonyl, carbomoyl, [N-(C₁ -C₄ alky)amino]carbonyl, [N, N-di(C₁ -C₄ alkyl)amino]carbonyl, cyano, nitro, mercapto, (C₁ -C₄ alkyl)thio, (C₁ -C₄ alkyl)sulfinyl, (C₁ -C₄ alkyl)sulfonyl, aminosulfonyl, [N-(C₁ -C₄ alkyl)amino]sulfonyl and [N, N-di(C₁ -C₄ alkyl)amino]sulfonyl; and

heteroaryl selected from:

a 5-membered monocyclic aromatic ring having one hetero atom

10 selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and

15 said heteroaryl being optionally substituted with one to three substituent(s) selected from X²⁰;

R^{139} and R^{140} are independently selected from:

hydrogen,

halo,

C₁ -C₄ alkyl,

20 phenyl optionally substituted with one to three substituent(s).

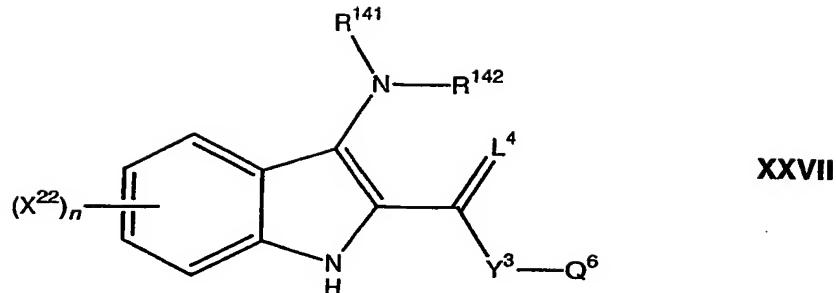
wherein said substituents are independently selected from halo, C₁ -C₄ alkyl, hydroxy, C₁ -C₄ alkoxy, amino, N-(C₁ -C₄ alkyl)amino and N, N-di(C₁ -C₄ alkyl)amino.

25 or R^{138} and R^{139} can form, together with the carbon atom to which they are attached, a $C_3 - C_7$ cycloalkyl ring:

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Patent No. 6,300,363. Such indole compounds have the formula shown below in formula **XXVII**:



and the pharmaceutically acceptable salts thereof,
wherein:

- 5 L^4 is oxygen or sulfur;
- 10 Y^3 is a direct bond or C_{1-4} alkylidene;
- 15 Q^6 is:
 (a) C_{1-6} alkyl or halosubstituted C_{1-6} alkyl, said alkyl being optionally substituted with up to three substituents independently selected from hydroxy, C_{1-4} alkoxy, amino and mono- or di- $(C_{1-4}$ alkyl)amino,
- 20 (b) C_{3-7} cycloalkyl optionally substituted with up to three substituents independently selected from hydroxy, C_{1-4} alkyl and C_{1-4} alkoxy,
- 25 (c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:
 (c-1) halo, C_{1-4} alkyl, halosubstituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstituted C_{1-4} alkoxy, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_{1-4}$ alkyl) $_2$, amino, mono- or di- $(C_{1-4}$ alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, $CO_2 (C_{1-4}$ alkyl), C_{1-4} alkyl-OH, C_{1-4} alkyl-OR 143 , $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl) $_2$ and —O—Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C_{1-4} alkyl, CF_3 , hydroxy, OR 143 , $S(O)_m R^{143}$, amino, mono- or di- $(C_{1-4}$ alkyl)amino and CN;
- 30 (d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three N atoms in addition to said heteroatom, and said aromatic

group being substituted with up to three substituents independently selected from:

(d-1) halo, C₁₋₄ alkyl, halosubstituted C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halosubstituted C₁₋₄ alkoxy, C₁₋₄ alkyl-OH, S(O)_m R¹⁴³, SO₂ NH₂, SO₂ N(C₁₋₄ alkyl)₂, amino, mono- or di-(C₁₋₄ alkyl)amino, NSO₂ R¹⁴³, NHC(O)R¹⁴³, CN, CO₂ H, CO₂ (C₁₋₄ alkyl), C₁₋₄ alkyl-OR¹⁴³, CONH₂, CONH(C₁₋₄ alkyl), CON(C₁₋₄ alkyl)₂, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF₃, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, OCF₃, SR¹⁴³, SO₂ CH₃, SO₂ NH₂, amino, C₁₋₄ alkylamino and NSO₂ R¹⁴³;

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

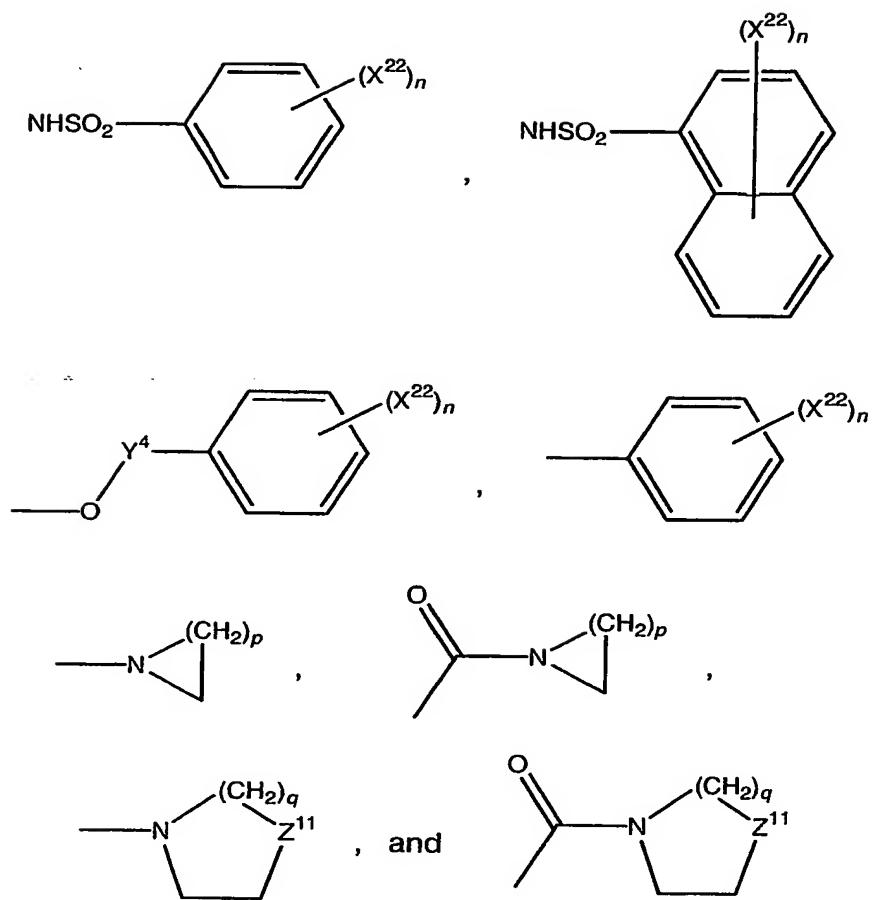
R¹⁴¹ is hydrogen or C₁₋₆ alkyl optionally substituted with a substituent selected independently from hydroxy, OR¹⁴³, nitro, amino, mono- or di-(C₁₋₄ alkyl)amino, CO₂ H, CO₂ (C₁₋₄ alkyl), CONH₂, CONH(C₁₋₄ alkyl) and CON(C₁₋₄ alkyl)₂;

R¹⁴² is:

- (a) hydrogen,
- (b) C₁₋₄ alkyl,
- (c) C(O)R¹⁴⁵,

wherein R¹⁴⁵ is selected from:

(c-1) C₁₋₂₂ alkyl or C₂₋₂₂ alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently selected from:
 (c-1-1) halo, hydroxy, OR¹⁴³, S(O)_m R¹⁴³, nitro, amino, mono- or di-(C₁₋₄ alkyl)amino, NSO₂ R¹⁴³, CO₂ H, CO₂ (C₁₋₄ alkyl), CONH₂, CONH(C₁₋₄ alkyl), CON(C₁₋₄ alkyl)₂, OC(O)R¹⁴³, thienyl, naphthyl and groups of the following formulae:



(c-2) C₁₋₂₂ alkyl or C₂₋₂₂ alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

5 (c-3) -Y⁵-C₃₋₇ cycloalkyl or -Y⁵-C₃₋₇ cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1) C₁₋₄ alkyl, hydroxy, OR¹⁴³, S(O)_m R¹⁴³, amino, mono- or di-(C₁₋₄ alkyl)amino, CONH₂, CONH(C₁₋₄ alkyl) and CON(C₁₋₄ alkyl)₂,

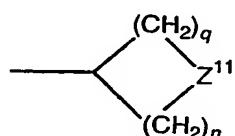
10 (c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

(c-4-1) halo, C₁₋₈ alkyl, C₁₋₄ alkyl-OH, hydroxy, C₁₋₈ alkoxy, halosubstituted C₁₋₈ alkyl, halosubstituted C₁₋₈ alkoxy, CN, nitro, S(O)_m R¹⁴³, SO₂ NH₂, SO₂ NH(C₁₋₄ alkyl), SO₂ N(C₁₋₄ alkyl)₂, amino, C₁₋₄ alkylamino, di-(C₁₋₄ alkyl)amino, CONH₂, CONH(C₁₋₄ alkyl), CON(C₁₋₄ alkyl)₂, OC(O)R¹⁴³, and phenyl optionally substituted with up to three substituents independently selected from halo, C₁₋₄ alkyl, hydroxy, OCH₃, CF₃, OCF₃, CN, nitro, amino, mono- or di-(C₁₋₄ alkyl)amino, CO₂ H, CO₂ (C₁₋₄ alkyl) and CONH₂,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C₁₋₈ alkyl, C₁₋₄ alkyl-OH, hydroxy, C₁₋₈ alkoxy, CF₃, OCF₃, CN, nitro, S(O)_m R¹⁴³, amino, mono- or di-(C₁₋₄ alkyl)amino, CONH₂, CONH(C₁₋₄ alkyl), CON(C₁₋₄ alkyl)₂, CO₂ H and CO₂ (C₁₋₄ alkyl), and —Y-phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, CF₃, OCF₃, CN, nitro, S(O)_m R¹⁴³, amino, mono- or di-(C₁₋₄ alkyl)amino, CO₂ H, CO₂ (C₁₋₄ alkyl), CONH₂, CONH(C₁₋₄ alkyl) and CON(C₁₋₄ alkyl)₂,

(c-6) a group of the following formula:

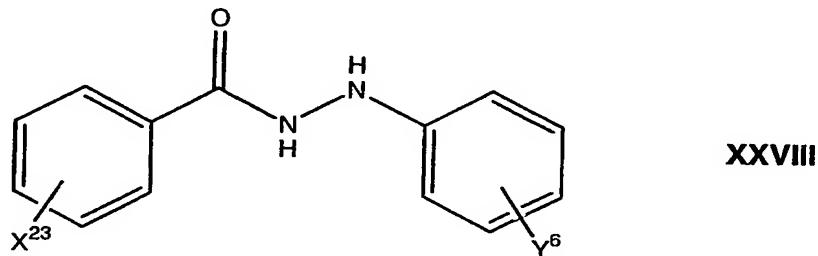


X²² is halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, halosubstituted C₁₋₄ alkoxy, S(O)_m R¹⁴³, amino, mono- or di-(C₁₋₄ alkyl)amino, NH₂SO₂ R¹⁴³, nitro, halosubstituted C₁₋₄ alkyl, CN, CO₂ H, CO₂ (C₁₋₄ alkyl), C₁₋₄ alkyl-OH, C₁₋₄ alkylOR¹⁴³, CONH₂, CONH(C₁₋₄ alkyl) or CON(C₁₋₄ alkyl)₂; R¹⁴³ is C₁₋₄ alkyl or halosubstituted C₁₋₄ alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;
 Z¹¹ is oxygen, sulfur or NR¹⁴⁴; and
 R¹⁴⁴ is hydrogen, C₁₋₆ alkyl, halosubstituted C₁₋₄ alkyl or -Y⁵-
 phenyl, said phenyl being optionally substituted with up to two substituents
 5 independently selected from halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, S(O)_m
 R¹⁴³, amino, mono- or di-(C₁₋₄ alkyl)amino, CF₃, OCF₃, CN and nitro;
 with the proviso that a group of formula -Y⁵-Q is not methyl or
 ethyl when X²² is hydrogen;

10 L⁴ is oxygen;
 R¹⁴¹ is hydrogen; and
 R¹⁴² is acetyl.

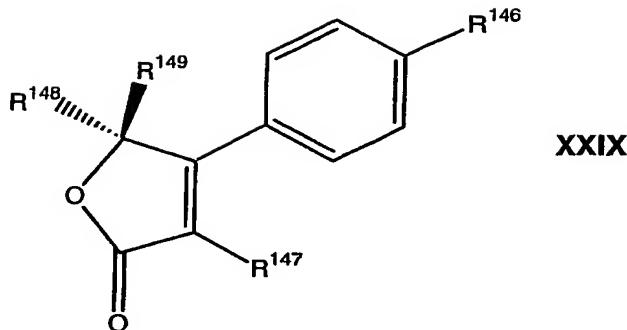
15 Materials that can serve as a cyclooxygenase-2 selective inhibitor
 of the present invention include aryl phenylhydrazides that are described
 in U.S. Patent No. 6,077,869. Such aryl phenylhydrazides have the
 formula shown below in formula XXVIII:



wherein:

20 X²³ and Y⁶ are selected from hydrogen, halogen, alkyl, nitro, amino or
 other oxygen and sulfur containing functional groups such as hydroxy,
 methoxy and methylsulfonyl.

25 Materials that can serve as a cyclooxygenase-2 selective inhibitor
 of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are
 described in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-
 ones have the formula shown below in formula XXIX:



or a pharmaceutical salt thereof,

wherein:

5 R^{146} is selected from the group consisting of SCH_3 , $—S(O)_2 CH_3$ and $—S(O)_2 NH_2$;

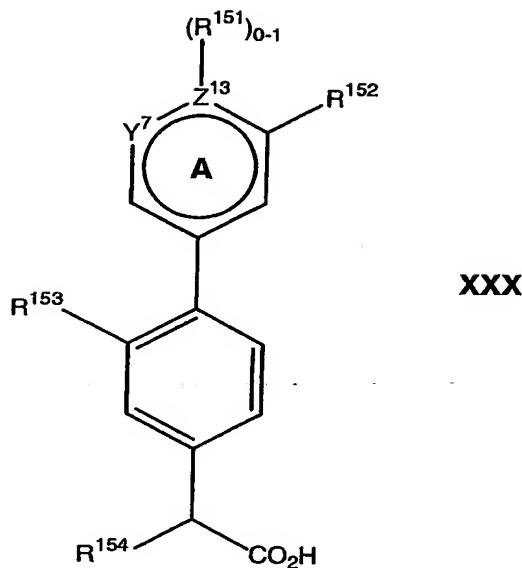
10 R^{147} is selected from the group consisting of OR^{150} , mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

15 R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

20 R^{148} is H, C_{1-4} alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

25 R^{149} is H, C_{1-4} alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula XXX:



or a pharmaceutically acceptable salt, ester or tautomer thereof,
wherein:

- 5 Z^{13} is C or N;
 when Z^{13} is N, R^{151} represents H or is absent, or is taken in
 conjunction with R^{152} as described below;
 when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the
 following characteristics:
- 10 (a) it is a linear chain of 3-4 atoms containing 0-2 double bonds,
 which can adopt an energetically stable transoid configuration and if a
 double bond is present, the bond is in the trans configuration,
 (b) it is lipophilic except for the atom bonded directly to ring A,
 which is either lipophilic or non-lipophilic, and
- 15 (c) there exists an energetically stable configuration planar with ring
 A to within about 15 degrees;
 or R^{151} and R^{152} are taken in combination and represent a 5- or 6-
 membered aromatic or non-aromatic ring D fused to ring A, said ring D
 containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an energetically stable configuration planar with ring A to within about 15 degrees;

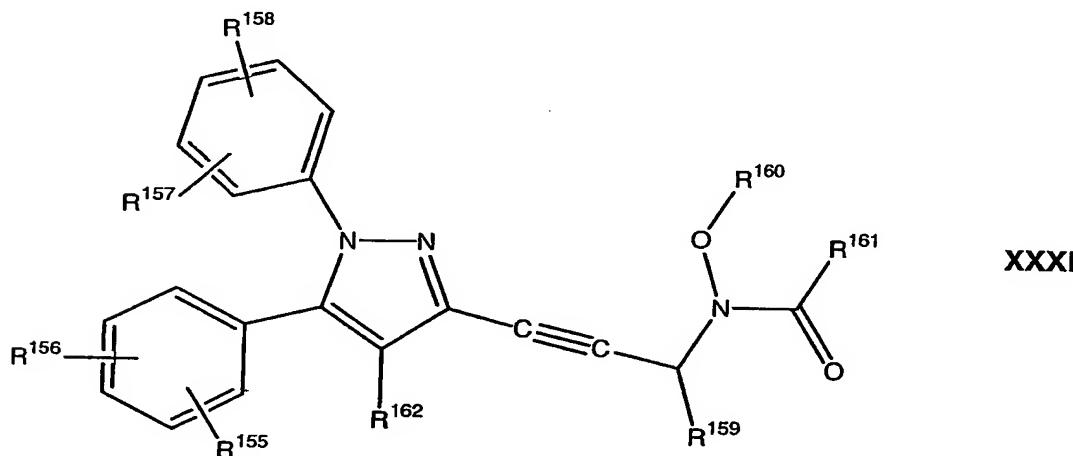
5 said ring D further being substituted with 1 R^a group selected from the group consisting of: C₁₋₂ alkyl, —OC₁₋₂ alkyl, —NHC₁₋₂ alkyl, —N(C₁₋₂ alkyl)₂, —C(O)C₁₋₂ alkyl, —S—C₁₋₂ alkyl and —C(S)C₁₋₂ alkyl;

Y⁷ represents N, CH or C—OC₁₋₃ alkyl, and when Z¹³ is N, Y⁷ can also represent a carbonyl group;

10 R¹⁵³ represents H, Br, Cl or F; and

R¹⁵⁴ represents H or CH₃.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula 15 shown below in formula XXXI:



wherein:

20 R¹⁵⁵, R¹⁵⁶, R¹⁵⁷, and R¹⁵⁸ are independently selected from the groups consisting of hydrogen, C₁₋₅ alkyl, C₁₋₅ alkoxy, phenyl, halo,

hydroxy, C₁₋₅ alkylsulfonyl, C₁₋₅ alkylthio, trihaloC₁₋₅ alkyl, amino, nitro and 2-quinolinylmethoxy;

5 R¹⁵⁹ is hydrogen, C₁₋₅ alkyl, trihaloC₁₋₅ alkyl, phenyl, substituted phenyl where the phenyl substitutents are halogen, C₁₋₅ alkoxy, trihaloC₁₋₅ alkyl or nitro or R¹⁵⁹ is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;

10 R¹⁶⁰ is hydrogen, C₁₋₅ alkyl, phenyl C₁₋₅ alkyl, substituted phenyl C₁₋₅ alkyl where the phenyl substitutents are halogen, C₁₋₅ alkoxy, trihaloC₁₋₅ alkyl or nitro, or R¹⁶⁰ is C₁₋₅ alkoxycarbonyl, phenoxy carbonyl, substituted 15 phenoxy carbonyl where the phenyl substitutents are halogen, C₁₋₅ alkoxy, trihaloC₁₋₅ alkyl or nitro;

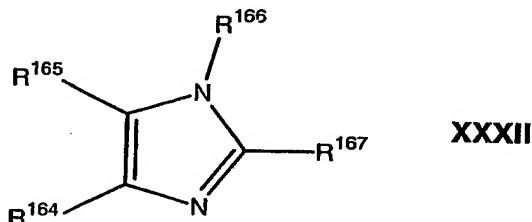
15 R¹⁶¹ is C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkyl where the substituents are halogen, trihaloC₁₋₅ alkyl, C₁₋₅ alkoxy, carboxy, C₁₋₅ alkoxycarbonyl, amino, C₁₋₅ alkylamino, diC₁₋₅ alkylamino, diC₁₋₅ alkylaminoC₁₋₅ alkylamino, C₁₋₅ alkylaminoC₁₋₅ alkylamino or a heterocycle containing 4-8 ring atoms where 20 one more of the ring atoms is nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with C₁₋₅ alkyl; or R¹⁶¹ is phenyl, substituted phenyl (where the phenyl substitutents are one or more of C₁₋₅ alkyl, halogen, C₁₋₅ alkoxy, trihaloC₁₋₅ alkyl or nitro), or R¹⁶¹ is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or

25 R¹⁶¹ is NR¹⁶³ R¹⁶⁴ where R¹⁶³ and R¹⁶⁴ are independently selected from hydrogen and C₁₋₅ alkyl or R¹⁶³ and R¹⁶⁴ may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C₁₋₅ alkyl;

30 R¹⁶² is hydrogen, C₁₋₅ alkyl, nitro, amino, and halogen; and pharmaceutically acceptable salts thereof.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-substituted imidazoles that are

described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula XXXII:



5

wherein:

R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

substituted phenyl;

10

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

substituted heteroaryl;

15

wherein the substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl and halogen, or substituted phenyl,

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

20

R^{166} is hydrogen, SEM, C_{1-5} alkoxy carbonyl, aryloxy carbonyl, aryl C_{1-5} alkoxy carbonyl, aryl C_{1-5} alkyl, phthalimido C_{1-5} alkyl, amino C_{1-5} alkyl, diamino C_{1-5} alkyl, succinimido C_{1-5} alkyl, C_{1-5} alkyl carbonyl, aryl carbonyl, C_{1-5} alkyl carbonyl C_{1-5} alkyl, aryloxy carbonyl C_{1-5} alkyl, heteroaryl C_{1-5} alkyl where the heteroaryl contains 5 to 6 ring atoms, or substituted aryl C_{1-5} alkyl,

25

wherein the aryl substituents are independently selected from one or more members of the group consisting of C₁₋₅ alkyl, C₁₋₅ alkoxy, halogen, amino, C₁₋₅ alkylamino, and diC₁₋₅ alkylamino;

R¹⁶⁷ is (A¹¹)_n -(CH¹⁶⁵)_q -X²⁴ wherein:

5 A¹¹ is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

10 X²⁴ is selected from the group consisting of hydrogen, hydroxy, halogen, vinyl, ethynyl, C₁₋₅ alkyl, C₃₋₇ cycloalkyl, C₁₋₅ alkoxy, phenoxy, phenyl, arylC₁₋₅ alkyl, amino, C₁₋₅ alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C₁₋₅ alkylaminocarbonyl, phenylaminocarbonyl, arylC₁₋₅ alkylaminocarbonyl, C₁₋₅ alkylthio, C₁₋₅ alkylsulfonyl, phenylsulfonyl, substituted sulfonamido,

15 wherein the sulfonyl substituent is selected from the group consisting of C₁₋₅ alkyl, phenyl, arylC₁₋₅ alkyl, thienyl, furanyl, and naphthyl; substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine, substituted ethynyl,

20 wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine chlorine and iodine,

substituted C₁₋₅ alkyl,

25 wherein the substituents are selected from the group consisting of one or more C₁₋₅ alkoxy, trihaloalkyl, phthalimido and amino, substituted phenyl,

wherein the phenyl substituents are independently selected from

one or more members of the group consisting of C₁₋₅ alkyl, halogen and C₁₋₅ alkoxy,

30 substituted phenoxy,

- wherein the phenyl substituents are independently selected from one or more members of the group consisting of C₁₋₅ alkyl, halogen and C₁₋₅ alkoxy,
- substituted C₁₋₅ alkoxy,
- 5 wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,
- substituted arylC₁₋₅ alkyl,
- wherein the alkyl substituent is hydroxyl,
- substituted arylC₁₋₅ alkyl,
- 10 wherein the phenyl substituents are independently selected from one or more members of the group consisting of C₁₋₅ alkyl, halogen and C₁₋₅ alkoxy,
- substituted amido,
- wherein the carbonyl substituent is selected from the group
- 15 consisting of C₁₋₅ alkyl, phenyl, arylC₁₋₅ alkyl, thienyl, furanyl, and naphthyl,
- substituted phenylcarbonyl,
- wherein the phenyl substituents are independently selected from one or members of the group consisting of C₁₋₅ alkyl, halogen and C₁₋₅ alkoxy,
- 20 substituted C₁₋₅ alkylthio,
- wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido,
- substituted C₁₋₅ alkylsulfonyl,
- wherein the alkyl substituent is selected from the group consisting
- 25 of hydroxy and phthalimido,
- substituted phenylsulfonyl,
- wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C₁₋₅ alkoxy and trifluoromethyl,
- 30 with the proviso:

if A^{11} is sulfur and X^{24} is other than hydrogen, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, C_{1-5} alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

if A^{11} is sulfur and q is 1, then X^{24} cannot be C_{1-2} alkyl;

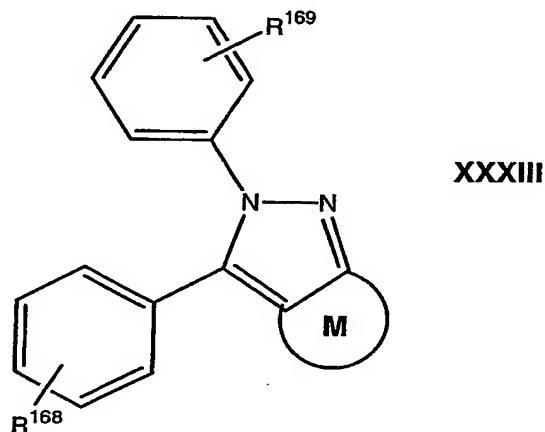
5 if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, C_{1-5} alkylsulfonyl or phenylsulfonyl;

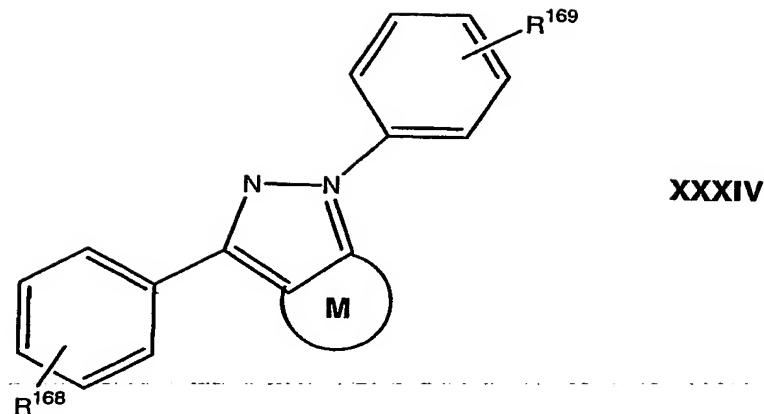
if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not SEM (2-(trimethylsilyl)ethoxymethyl);

10 if n is 0 and q is 0, then X^{24} cannot be hydrogen; and pharmaceutically acceptable salts thereof.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcy cloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969.

15 Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas XXXIII and XXXIV:

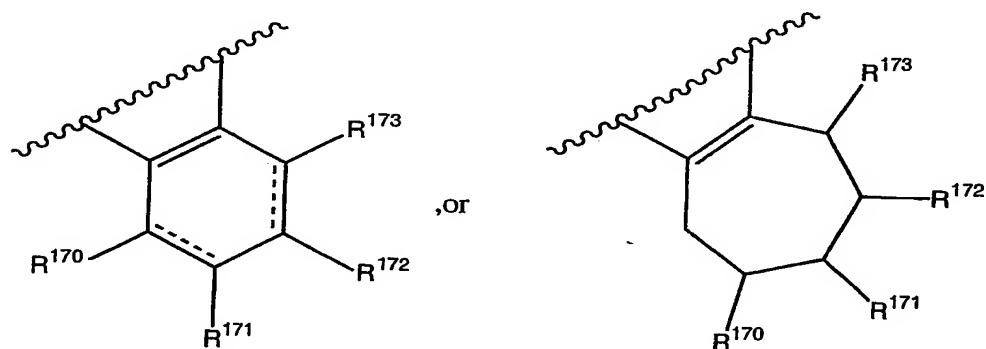




wherein:

5 R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, $(C_1 - C_6)$ alkyl, $(C_1 - C_6)$ alkoxy, nitro, amino, hydroxy, trifluoro, $-S(C_1 - C_6)$ alkyl, $-SO(C_1 - C_6)$ alkyl and $-SO_2(C_1 - C_6)$ alkyl; and the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:

10



wherein:

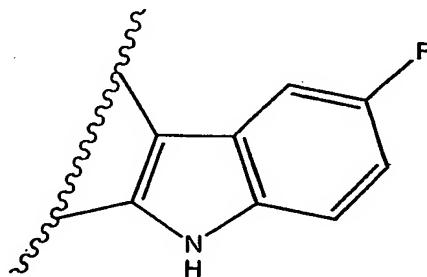
15 R^{170} is selected from the group consisting of hydrogen, halogen, hydroxy and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of $—OCOCH_2—$, $—ONH(CH_3)COCH_2—$, $—OCOCH.dbd.$ and $—O—$;

5 R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxy, carbonyl, amino, $(C_1 - C_6)$ alkyl, $(C_1 - C_6)$ alkoxy, $=NOH$, $—NR^{174} R^{175}$, $—OCH_3$, $—OCH_2 CH_3$, $—OSO_2 NHCO_2 CH_3$, $=CHCO_2 CH_2 CH_3$, $—CH_2 CO_2 H$, $—CH_2 CO_2 CH_3$, $—CH_2 CO_2 CH_2 CH_3$, $—CH_2 CON(CH_3)_2$, $—CH_2 CO_2 NHCH_3$, $—CHCHCO_2 CH_2 CH_3$, $—OCON(CH_3)OH$, $—C(COCH_3)_2$, di $(C_1 - C_6)$ alkyl and di $(C_1 - C_6)$ alkoxy;

10 R^{173} is selected from the group consisting of hydrogen, halogen, hydroxy, carbonyl, amino, $(C_1 - C_6)$ alkyl, $(C_1 - C_6)$ alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxy, amino, $(C_1 - C_6)$ alkyl and $(C_1 - C_6)$ alkoxy;

15 or R^{172} and R^{173} taken together form a moiety selected from the group consisting of $—O—$ and



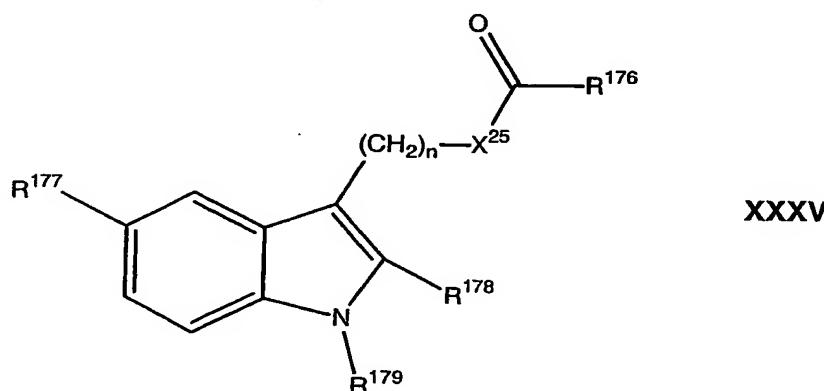
20 R^{174} is selected from the group consisting of hydrogen, OH, $—OCOCH_3$, $—COCH_3$ and $(C_1 - C_6)$ alkyl; and

R^{175} is selected from the group consisting of hydrogen, OH, $—OCOCH_3$, $—COCH_3$, $(C_1 - C_6)$ alkyl, $—CONH_2$ and $—SO_2 CH_3$;
with the proviso that

25 if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

pharmaceutically acceptable salts, esters and pro-drug forms thereof.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890. Such compounds have the general formula shown below in formula XXXV:



10

wherein:

R¹⁷⁶ is C₁ to C₆ alkyl, C₁ to C₆ branched alkyl, C₄ to C₈ cycloalkyl, C₁ to C₆ hydroxyalkyl, branched C₁ to C₆ hydroxyalkyl, hydroxy substituted C₄ to C₈ aryl, primary, secondary or tertiary C₁ to C₆ alkylamino, primary, 15 secondary or tertiary branched C₁ to C₆ alkylamino, primary, secondary or tertiary C₄ to C₈ arylamino, C₁ to C₆ alkylcarboxylic acid, branched C₁ to C₆ alkylcarboxylic acid, C₁ to C₆ alkylester, branched C₁ to C₆ alkylester, C₄ to C₈ aryl, C₄ to C₈ arylcarboxylic acid, C₄ to C₈ arylester, C₄ to C₈ aryl 20 substituted C₁ to C₆ alkyl, C₄ to C₈ heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C₄ to C₈ heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R¹⁷⁷ is C₁ to C₆ alkyl, C₁ to C₆ branched alkyl, C₄ to C₈ cycloalkyl, C₄ to C₈ aryl, C₄ to C₈ aryl-substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to

C₆ branched alkoxy, C₄ to C₈ aryloxy, or halo-substituted versions thereof or R¹⁷⁷ is halo where halo is chloro, fluoro, bromo, or iodo;

R¹⁷⁸ is hydrogen, C₁ to C₆ alkyl or C₁ to C₆ branched alkyl;

R¹⁷⁹ is C₁ to C₆ alkyl, C₄ to C₈ aroyl, C₄ to C₈ aryl, C₄ to C₈

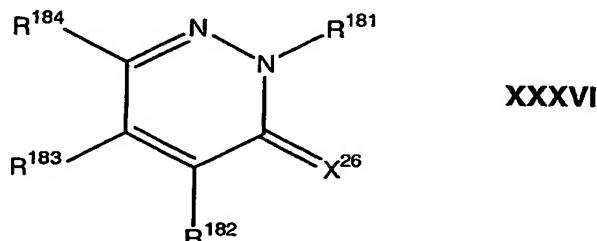
5 heterocyclic alkyl or aryl with O, N or S in the ring, C₄ to C₈ aryl-substituted C₁ to C₆ alkyl, alkyl-substituted or aryl-substituted C₄ to C₈ heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted C₄ to C₈ aroyl, or alkyl-substituted C₄ to C₈ aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

10 n is 1, 2, 3, or 4; and

X²⁵ is O, NH, or N—R¹⁸⁰, where R¹⁸⁰ is C₁ to C₆ alkyl or C₁ to C₆ branched alkyl.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyridazinone compounds that are

15 described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula XXXVI:



20 or a pharmaceutically acceptable salt, ester, or prodrug thereof,

wherein:

X²⁶ is selected from the group consisting of O, S, —NR¹⁸⁵, —NOR^a, and —NNR^b R^c;

25 R¹⁸⁵ is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

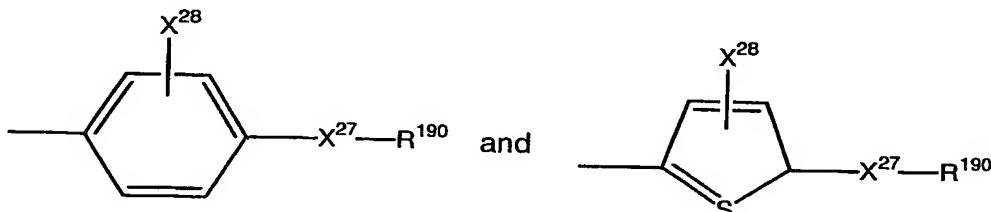
R^a, R^b, and R^c are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

R^{181} is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, 5 alkylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, $-(CH_2)_n C(O)R^{186}$, $-(CH_2)_n CH(OH)R^{186}$, $-(CH_2)_n C(NOR^d)R^{186}$, $-(CH_2)_n CH(NOR^d)R^{186}$, $-(CH_2)_n CH(NR^d R^e)R^{186}$, $-R^{187} R^{188}$, $-(CH_2)_n C\equiv CR^{188}$, $-(CH_2)_n [CH(CX^{26'})_m (CH_2)_p R^{188}]$, $-(CH_2)_n (CX^{26'})_m (CH_2)_p R^{188}$, and $-(CH_2)_n (CHX^{26'})_m (CH_2)_p R^{188}$;
 R^{186} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, 10 haloalkynyl, heterocyclic, and heterocyclic alkyl;
 R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;
 R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, 15 heterocyclic, and heterocyclic alkyl;
 R^d and R^e are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;
 $X^{26'}$ is halogen;
20 m is an integer from 0-5;
 n is an integer from 0-10; and
 p is an integer from 0-10; and
 R^{182} , R^{183} , and R^{184} are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, 25 alkoxyminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl,
30

carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y^8 , and Z^{14} ;

5 provided that one of R^{182} , R^{183} , or R^{184} must be Z^{14} , and further provided that only one of R^{182} , R^{183} , or R^{184} is Z^{14} ;

Z^{14} is selected from the group consisting of:



X^{27} is selected from the group consisting of $S(O)_2$, $S(O)(NR^{191})$, $S(O)$, $Se(O)_2$, $P(O)(OR^{192})$, and $P(O)(NR^{193}R^{194})$;

15 X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, $-NHNH_2$, and $-NCHN(R^{191})R^{192}$;

20 R^{191} , R^{192} , R^{193} , and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188} ;

25 Y^8 is selected from the group consisting of $-OR^{195}$, $-SR^{195}$, $-C(R^{197})(R^{198})R^{195}$, $-C(O)R^{195}$, $-C(O)OR^{195}$, $-N(R^{197})C(O)R^{195}$, $-NC(R^{197})R^{195}$, and $-N(R^{197})R^{195}$;

R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl,

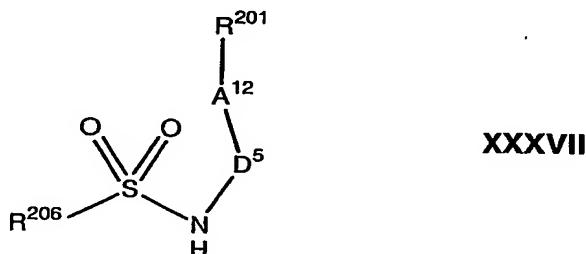
cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and NR¹⁹⁹ R²⁰⁰; and

R¹⁹⁷, R¹⁹⁸, R¹⁹⁹, and R²⁰⁰ are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

5

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948. Such benzosulphonamide derivatives have the formula shown below in formula XXXVII:

10

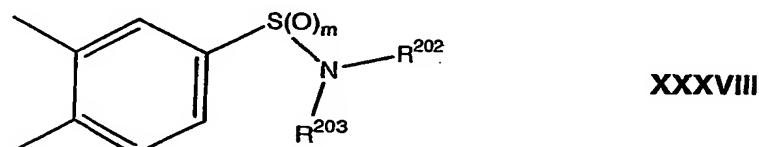


herein:

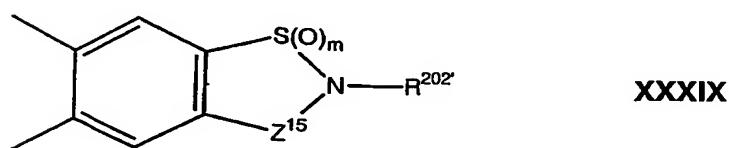
A¹² denotes oxygen, sulphur or NH;

15 R²⁰¹ denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF₃ or alkoxy;

D⁵ denotes a group of formula XXXVIII or XXXIX:



or



R^{202} and R^{203} independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical $(CH_2)_n - X^{29}$; or

5 R^{202} and R^{203} together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n - X^{29}$, R^{202} denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n - X^{29}$,

10 wherein:

X^{29} denotes halogen, NO_2 , $-OR^{204}$, $-COR^{204}$, $-CO_2 R^{204}$, $-OCO_2 R^{204}$, $-CN$, $-CONR^{204} OR^{205}$, $-CONR^{204} R^{205}$, $-SR^{204}$, $-S(O)R^{204}$, $-S(O)_2 R^{204}$, $-NR^{204} R^{205}$, $-NHC(O)R^{204}$, $-NHS(O)_2 R^{204}$; Z^{15} denotes $-CH_2 -$, $-CH_2 - CH_2 -$, $-CH_2 - CH_2 - CH_2 -$, $-CH_2 -$, $CH=CH -$, $CH=CH - CH_2 -$, $-CH_2 - CO -$, $-CO - CH_2 -$, $-NHCO -$, $-CONH -$, $-NHCH_2 -$, $-CH_2 NH -$, $-N=CH -$, $-NHCH -$, $-CH_2 - CH_2 - NH -$, $-CH=CH -$, $>N - R^{203}$, $>C=O$, $>S(O)_m$;

15 R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

20 n is an integer from 0 to 6;

R^{206} is a straight-chained or branched C_{1-4} -alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3 ; and

25 m denotes an integer from 0 to 2;

with the proviso that A^{12} does not represent O if R^{206} denotes CF_3 ; and the pharmaceutically acceptable salts thereof.

30 Cox-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Patent Nos. 6,169,188, 6,020,343, 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and

5,945,539 (oxazole derivatives); and U.S. Patent No. 6,359,182 (C-nitroso compounds).

5 Cyclooxygenase-2 selective inhibitors that are useful in the present invention can be supplied by any source as long as the cyclooxygenase-2-selective inhibitor is pharmaceutically acceptable. Cyclooxygenase-2-selective inhibitors can be isolated and purified from natural sources or can be synthesized. Cyclooxygenase-2-selective inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

10 In some embodiments of the invention, glucosamine is also present in the combination. Glucosamine that is useful in the present invention may be obtained from any source of glucosamine. Glucosamine is 2-amino-2-deoxyglucose, and is an amino sugar that is found generally in chitin, cell membranes and mucopolysaccharides (e.g., as a component of cartilage). The glucosamine can be isolated and purified from natural sources, purchased from commercial suppliers, or synthesized by any method suitable for the synthesis of pharmaceutically acceptable glucosamine. Useful sources of glucosamine include, without limitation, glucosamine, glucosamine salts of hydrochloric, iodic, sulfuric, phosphoric, 15 or other pharmaceutically acceptable acid, such as glucosamine-2-sulfate, glucosamine-3-sulfate, glucosamine-6-sulfate, glucosamine-2,3-disulfate, glucosamine-2,6-disulfate, glucosamine-3,6-disulfate, glucosamine-3,4,6-trisulfate, glucosamine pentaacetate, glucosamine-1-phosphate, glucosamine-6-phosphate, N-acetylglucosamine-6-phosphate, N- 20 acetylglucosamine-1-phosphate, N-acetyl-D-glucosamine, and uridine diphosphate (UDP)-N-acetylglucosamine. Preferred sources of glucosamine include D(+) -glucosamine, glucosamine sulfate, glucosamine hydroiodide, glucosamine hydrochloride, and N-acetyl glucosamine.

25 Glucosamine can also be supplied by the isolation and purification of glucosamine from hydrolysis products and other derivatives of chitin which contain glucosamine. The glucosamine can also contain mixtures of two or more of any of the materials described above. A preferred type of

glucosamine that is useful in the present invention comprises substantially pure D-glucosamine. One source of such pure D-glucosamine is D(+)-glucosamine, available from Sigma-Aldrich, St. Louis, MO.

As used herein, the term "purified" means partially purified and/or completely purified. Thus a "purified composition" may be either partially purified or completely purified. For example, chondroitin sulfate or glucosamine from a natural source, or an extract of a naturally occurring cyclooxygenase-2 inhibitor, may be partially purified or completely purified. Such materials can also be synthesized.

10 The chondroitin sulfate and the glucosamine that are useful in the subject method can be of any purity and quality that are pharmaceutically acceptable.

15 In the present method, a subject in need of prevention or treatment of pain, inflammation or inflammation-associated disorder is treated with an amount of chondroitin sulfate and an amount of a Cox-2 selective inhibitor, where the amount of the chondroitin sulfate, when administered with an amount of the Cox-2 selective inhibitor, together provide a dosage or amount of the combination that is sufficient to constitute a pain or inflammation suppressing treatment or prevention effective amount.

20 As used herein, an "effective amount" means the dose or effective amount to be administered to a patient and the frequency of administration to the subject which is readily determined by one or ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances. The dose or effective amount to be
25 administered to a patient and the frequency of administration to the subject can be readily determined by one of ordinary skill in the art by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including but not
30 limited to, the potency and duration of action of the compounds used; the nature and severity of the illness to be treated as well as on the sex, age,

weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

5 The phrase "therapeutically-effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies.

Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

10 In the present method, the amount of chondroitin sulfate that is used is such that, when administered with the cyclooxygenase-2 selective inhibitor, it is sufficient to constitute a therapeutically effective amount of the combination. Such an amount can also be described in terms of being a pain or inflammation suppressing treatment or prevention effective 15 amount of the combination.

It is preferred that the amount of chondroitin sulfate that is used for treatment is within a range of from about 5 mg/day per kilogram of body weight of the subject (mg/day·kg) to about 150 mg/day·kg. It is more preferred that the amount is from about 8 mg/kg-day to about 100 20 mg/day·kg, even more preferred that it is from about 10 mg/day·kg to about 30 mg/day·kg, and yet more preferred that it is from about 10 mg/day·kg to about 20 mg/day·kg.

25 The amount of Cox-2 selective inhibitor that is used in the subject method may be an amount that, when administered with the chondroitin sulfate, is sufficient to constitute a pain or inflammation suppressing treatment or prevention effective amount of the combination. In the present method, the amount of Cox-2 selective inhibitor that is used in the novel method of treatment preferably ranges from about 0.01 to about 100 milligrams per day per kilogram of body weight of the subject (mg/day·kg), 30 more preferably from about 0.1 to about 50 mg/day·kg, even more preferably from about 1 to about 20 mg/day·kg.

When the Cox-2 selective inhibitor comprises rofecoxib, it is preferred that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more preferably from about 0.18 to about 0.4 mg/day·kg.

5 When the Cox-2 selective inhibitor comprises etoricoxib, it is preferred that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more preferably from about 0.8 to about 4 mg/day·kg.

10 When the Cox-2 selective inhibitor comprises celecoxib, it is preferred that the amount used is within a range of from about 1 to about 10 mg/day·kg, even more preferably from about 1.4 to about 8.6 mg/day·kg, and yet more preferably from about 2 to about 3 mg/day·kg.

15 In the present method, and in the subject compositions, chondroitin sulfate is administered with, or is combined with, a Cox-2 selective inhibitor. It is preferred that the weight ratio of the amount of chondroitin sulfate to the amount of Cox-2 selective inhibitor that is administered to the subject is within a range of from about 0.05:1 to about 15,000:1, more preferred is a range of from about 0.15:1 to about 1000:1, even more preferred is a range of from about 0.5:1 to about 20:1.

20 In an embodiment of the present method, glucosamine can be added as a component of the combination with the cyclooxygenase-2 selective inhibitor and the chondroitin sulfate. The amount of glucosamine that is used in the novel method of treatment preferably ranges from about 0.1 to about 500 milligrams per day per kilogram of body weight of the subject (mg/day·kg), more preferably from about 0.5 to about 100 mg/day·kg, even more preferably from about 1 to about 50 mg/day·kg, yet more preferably from about 5 to about 35 mg/day·kg, and even more preferably from about 15 to about 25 mg/day·kg.

25 The combination of chondroitin sulfate and a Cox-2 selective inhibitor, optionally with glucosamine, can be supplied in the form of a novel therapeutic composition that is believed to be within the scope of the

present invention. The relative amounts of each component in the therapeutic composition may be varied and may be as described just above. The chondroitin sulfate and Cox-2 selective inhibitor, and the glucosamine when it is present, that are described above can be provided 5 in the therapeutic composition so that the preferred amounts of each of the components are supplied by a single dosage; a single capsule for example, or, by up to four, or more, single dosage forms.

When the novel combination is supplied along with a pharmaceutically acceptable carrier, a pharmaceutical composition is 10 formed. A pharmaceutical composition of the present invention is directed to a composition suitable for the prevention or treatment of pain, inflammation and/or an inflammation-associated disorder. The pharmaceutical composition comprises a pharmaceutically acceptable carrier and a combination selected from chondroitin sulfate and 15 cyclooxygenase-2 selective inhibitors, and optionally with glucosamine. Pharmaceutically acceptable carriers include, but are not limited to, physiological saline, Ringer's, phosphate solution or buffer, buffered saline, and other carriers known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. 20 Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective.

The term "pharmacologically effective amount" shall mean that 25 amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

The term "pharmaceutically acceptable" is used herein to mean that 30 the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to,

appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

Also included in the combination of the invention are the isomeric forms and tautomers and the pharmaceutically-acceptable salts of chondroitin sulfate, glucosamine and cyclooxygenase-2 selective inhibitors. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β -hydroxybutyric, galactaric and galacturonic acids.

Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to, appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIA) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines

and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, megumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art
5 by conventional means from the corresponding compound of the present invention.

The method and combination of the present invention are useful for, but not limited to, the prevention, inhibition, and treatment of pain and/or inflammation in a subject, and for treatment of inflammation-associated
10 disorders, such as for use as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, combinations of the invention would be useful to treat arthritis, including, but not limited to, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.
15 Such combinations of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, and skin related conditions such as psoriasis, eczema, burns and dermatitis.

Combinations of the invention also would be useful to treat
20 gastrointestinal conditions such as inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as colorectal cancer. Combinations of the invention would be useful in treating inflammation in diseases and conditions such as herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound
25 healing, vaginitis, candidiasis, lumbar spondylarhrosis, lumbar spondylarthritis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarthritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis,
30

hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

5 Compositions having the novel combination would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compositions would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compositions would also be useful for the treatment of certain central nervous system disorders such as cortical dementias

10 including Alzheimer's disease. The combinations of the invention are also useful as anti-inflammatory agents, such as for the treatment of arthritis.

15 As used herein, the terms "pain, inflammation or inflammation-associated disorder", and "cyclooxygenase-2 mediated disorder" are meant to include, without limitation, each of the symptoms or diseases that is mentioned above.

20 The present method includes the treatment and/or prevention of a cyclooxygenase-2 mediated disorder in a subject, where the method comprises treating the subject having or susceptible to the disorder with a therapeutically-effective amount of a combination of chondroitin sulfate and a compound or salt of any of the cyclooxygenase-2 selective inhibitors that are described in this specification. This method is particularly useful where the cyclooxygenase-2 mediated disorder is inflammation, arthritis, pain, or fever.

25 The terms "treating" or "to treat" mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of or prevention of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described above. Besides being useful for human treatment,

30 these combinations are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

The term "subject" for purposes of treatment includes any human or animal subject who is in need of the prevention of, or who has pain, inflammation and/or any one of the known inflammation-associated disorders. The subject is typically a human subject.

5 For methods of prevention, the subject is any human or animal subject, and preferably is a subject that is in need of prevention and/or treatment of pain, inflammation and/or an inflammation-associated disorder. The subject may be a human subject who is at risk for pain and/or inflammation, or for obtaining an inflammation-associated disorder, 10 such as those described above. The subject may be at risk due to genetic predisposition, sedentary lifestyle, diet, exposure to disorder-causing agents, exposure to pathogenic agents and the like.

15 The pharmaceutical compositions may be administered enterally and parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

20 The phrases "combination therapy", "co-administration", "administration with", or "co-therapy", in defining the use of a cyclooxygenase-2 inhibitor agent and glucosamine, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well 25 to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule or dosage device having a fixed ratio of these active agents or in multiple, separate capsules or dosage devices for each agent, where the separate capsules or dosage devices can be taken together contemporaneously, or taken within a 30 period of time sufficient to receive a beneficial effect from both of the constituent agents of the combination.

The phrase "therapeutically-effective" and "effective for the treatment, prevention, or inhibition", are intended to qualify the amount of each agent for use in the combination therapy which will achieve the goal of improvement in inflammation severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

5 Although the combination of the present invention may include administration of a chondroitin sulfate component and a cyclooxygenase-2 selective inhibitor component within an effective time of each respective 10 component, it is preferable to administer both respective components contemporaneously, and more preferable to administer both respective components in a single delivery dose.

In particular, the combinations of the present invention can be 15 administered orally, for example, as tablets, coated tablets, dragees, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any 20 method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are 25 suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for 30 example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay

material such as glyceryl monostearate or glyceryl distearate may be employed.

5 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

10 Aqueous suspensions can be produced that contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-15 occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and 20 a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

25 The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

30 Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

- 5 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.
- 10 Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

- 15 Syrups and elixirs containing the novel combination may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

- 20 The subject combinations can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or oilogenous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above, or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol.
- 25 Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

30 The subject combination can also be administered by inhalation, in the form of aerosols or solutions for nebulizers, or rectally, in the form of

suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols.

5 The novel compositions can also be administered topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions.

10 Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage has been described above, although the limits that were identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

15 Various delivery systems include capsules, tablets, and gelatin capsules, for example.

20 The present invention further comprises kits that are suitable for use in performing the methods of treatment, prevention or inhibition described above. In one embodiment, the kit contains a first dosage form comprising chondroitin sulfate in one or more of the forms identified above and a second dosage form comprising one or more of the

25 cyclooxygenase-2 selective inhibitors or prodrugs thereof identified above, in quantities sufficient to carry out the methods of the present invention.

30 Preferably, the first dosage form and the second dosage form together comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder. In another embodiment, a third dosage form comprising glucosamine is also present. Preferably, the first dosage form, the second dosage form, and the third dosage form together comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder.

The following examples describe embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent

to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow
5 the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

COMPARATIVE EXAMPLE 1

This example shows the preparation of celecoxib.

Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-
10 dione.

Following the disclosure provided in U.S. Patent No. 5,760,068, 4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5
15 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 x 75 mL ethyl acetate. The extracts were dried over MgSO₄, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further
20 purification.

Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol, 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine
25 hydrochloride was added. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid, having a melting point (mp) of
30 157°-159°C; and a calculated composition of C₁₇ H₁₄ N₃ O₂ SF₃ : C, 53.54; H, 3.70; N, 11.02. The composition that was found by analysis was: C, 53.17; H, 3.81; N, 10.90.

EXAMPLE 2

This illustrated the production of a composition containing celebrex and chondroitin sulfate and of a pharmaceutical composition containing the combinations.

5 A therapeutic composition of the present invention can be formed by intermixing chondroitin sulfate A (600 g, available as Product Number C-8529, from Sigma-Aldrich, St. Louis, MO), chondroitin sulfate C (600 g, available as Product Number C-4384, from Sigma Aldrich, St. Louis, MO), and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-
10 yl]benzenesulfonamide (200 g, as produced in Comparative Example 1, or as available from Pharmacia Corporation, St. Louis, MO), in a laboratory mill or mixing device suitable for intimate mixing of powders without substantial generation of shear or temperature sufficient to degrade either of the two compounds. After mixing, the combination of celecoxib and
15 chondroitin sulfate form a therapeutic composition that is sufficient for the production of about 1000 human single dose units. Each single dose unit contains about 1,200 mg of chondroitin sulfate and about 200 mg of celecoxib.

20 If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains 1,200 mg of chondroitin sulfate and 200 mg celecoxib.

25 Alternatively, the chondroitin sulfate and the celecoxib may be dissolved into a liquid carrier, such as, for example, normal saline solution, to form a pharmaceutical composition suitable for human consumption. A single dosage of the liquid pharmaceutical composition for human use would be a volume sufficient to provide 1,200 mg of chondroitin sulfate
30 and 200 mg of celecoxib.

Therapeutic and pharmaceutical compositions comprising a combination of any of the cyclooxygenase-2 selective inhibitors and any of

the sources of chondroitin sulfate that are described above can be formed by similar methods.

EXAMPLE 3

5 This illustrates the production of a composition containing celebrex, chondroitin sulfate and glucosamine and of a pharmaceutical composition containing the combination.

10 A therapeutic composition of the present invention can be formed by intermixing chondroitin sulfate A (600 g, available as Product Number C-8529, from Sigma-Aldrich, St. Louis, MO), chondroitin sulfate C (600 g, available as Product Number C-4384, from Sigma Aldrich, St. Louis, MO), glucosamine (1500 g, available as D(+)-glucosamine hydrochloride, from Sigma-Aldrich, St. Louis, MO) and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Comparative Example 1, or as available from Pharmacia Corporation, 15 St. Louis, MO), in a laboratory mill or mixing device suitable for intimate mixing of powders without substantial generation of shear or temperature sufficient to degrade either of the three active compounds. After mixing, the combination of celecoxib, chondroitin sulfate and glucosamine form a therapeutic composition that is sufficient for the production of about 1000 20 human single dose units.

25 If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains 1200 mg of chondroitin sulfate, 1500 mg of glucosamine and 200 mg celecoxib.

30 Alternatively, the combination of chondroitin sulfate, glucosamine and the celecoxib may be dissolved into a liquid carrier, such as, for example, normal saline solution, to form a pharmaceutical composition suitable for human consumption. A single dosage of the liquid pharmaceutical composition for human use would be a volume sufficient to

provide 1200 mg of chondroitin sulfate, 1500 mg of glucosamine and 200 mg of celecoxib.

5 Therapeutic and pharmaceutical compositions comprising a combination of any of the cyclooxygenase-2 selective inhibitors and any of the sources of chondroitin sulfate and glucosamine that are described above can be formed by similar methods.

EXAMPLE 4

This illustrates the evaluation of the biological efficacy of a therapeutic composition of chondroitin sulfate and celecoxib.

10 A therapeutic composition containing chondroitin sulfate and celecoxib is prepared as described in Example 2. The biological efficacy of the composition is determined by a rat carrageenan foot pad edema test and by a rat carrageenan-induced analgesia test.

Rat Carrageenan Foot Pad Edema Test:

15 The carrageenan foot edema test is performed with materials, reagents and procedures essentially as described by Winter, *et al.*, (*Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962)). Male Sprague-Dawley rats are selected in each group so that the average body weight is as close as possible. Rats are fasted with free access to water for over sixteen hours
20 prior to the test. The rats are dosed orally (1 mL) with compounds suspended in a carrier vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with only the carrier vehicle alone. One hour later, a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline is administered to one foot and the volume of the injected foot is
25 measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot is again measured. The average foot swelling in a group of drug-treated animals is compared with that of a group of placebo-treated animals and the percentage inhibition of edema
30 is determined (Ottermess and Bliven, *Laboratory Models for Testing NSAIDS, in Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The percent inhibition shows the percent decrease from control

paw volume determined in this procedure. The data are expected to show that the combination of chondroitin sulfate and celecoxib provided effective anti-inflammatory activity.

Rat Carrageenan-induced Analgesia Test:

- 5 The analgesia test using rat carrageenan is performed with materials, reagents and procedures essentially as described by Hargreaves, *et al.*, (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats are treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats are placed in a 10 special PLEXIGLAS® container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty-minute period, thermal stimulation is begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell will turn off the lamp and timer when the light is interrupted by paw withdrawal. 15 The time until the rat withdraws its foot is then measured. The withdrawal latency in seconds is determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal is determined. Results are expected to show that combination of chondroitin sulfate and celecoxib provided effective analgesic activity.

20 EXAMPLE 5

This illustrates the biological efficacy of a therapeutic composition of chondroitin sulfate and celecoxib for the treatment of collagen-induced arthritis in mice.

- 25 A therapeutic composition containing chondroitin sulfate and celecoxib is prepared as described in Example 2. The biological efficacy of the composition is determined by induction and assessment of collagen-induced arthritis in mice.

30 Arthritis is induced in 8-12 week old male DBA/1 mice by injection of 50 µg of chick-type II collagen (CII) in complete Freunds adjuvant (Sigma) on day 0 at the base of the tail as described in [J. Stuart, *Annual Rev. Immunol.*, 2, 199 (1984)]. Compounds are prepared as a suspension in 0.5% methylcellulose (Sigma, St. Louis, Mo.), and 0.025% Tween 20

(Sigma). The cyclooxygenase-2 inhibitor (celecoxib, as described in Comparative Example 1), and chondroitin sulfate (available from Sigma-Aldrich, St. Louis, MO) are administered alone or in combination as a therapeutic composition as described in Example 2. The compounds are administered in non-arthritic animals by gavage in a volume of 0.1 ml beginning on day 20 post collagen injection and continuing daily until final evaluation on day 55. Animals are boosted on day 21 with 50 µg of collagen (CII) in incomplete Freunds adjuvant. The animals are subsequently evaluated several times each week for incidence and severity of arthritis until day 56. Any animal with paw redness or swelling is counted as arthritic. Scoring of severity is carried out using a score of 0-3 for each paw (maximal score of 12/mouse) as described in P. Wooley, *et al.*, *Trans. Proc.*, 15, 180 (1983). The animals are measured for incidence of arthritis and severity in the animals where arthritis was observed. The incidence of arthritis is determined at a gross level by observing the swelling or redness in the paw or digits. Severity is measured with the following guidelines. Briefly, animals displaying four normal paws, *i.e.*, no redness or swelling are scored 0. Any redness or swelling of digits or the paw are scored as 1. Gross swelling of the whole paw or deformity is scored as 2. Ankylosis of joints is scored as 3.

Histological Examination of Paws:

In order to verify the gross determination of a non-arthritic animal, a histological examination can be performed. Paws from animals sacrificed at the end of the experiment are removed, fixed and decalcified as previously described [R. Jonsson, *J. Immunol. Methods*, 88, 109 (1986)]. Samples are paraffin embedded, sectioned, and stained with hematoxylin and eosin by standard methods. Stained sections are examined for cellular infiltrates, synovial hyperplasia, and bone and cartilage erosion.

It is expected that results will show that the combination of a cyclooxygenase-2 selective inhibitor with chondroitin sulfate was an efficacious treatment for collagen-induced arthritis in mice.

It is expected that Examples 4 and 5 can be repeated with compositions comprising chondroitin sulfate, glucosamine and a cyclooxygenase-2 selective inhibitor, such as are described in Example 3, with the results showing that the combination provides effective anti-inflammatory activity, effective analgesic activity, and is an efficacious treatment of collagen-induced arthritis in mice.

5 All references cited in this specification, including without limitation, all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, 10 periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants 15 reserve the right to challenge the accuracy and pertinency of the cited references.

In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is 20 intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

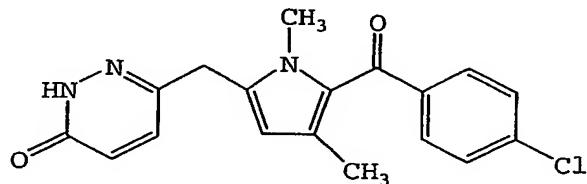
WHAT IS CLAIMED IS:

1. A method for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering chondroitin sulfate and a cyclooxygenase-2 selective inhibitor or prodrug thereof to the subject.
5
2. The method according to claim 1, wherein the administration of the chondroitin sulfate and the cyclooxygenase-2 selective inhibitor or prodrug thereof together comprises an effective method for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder.
10
3. The method according to claim 1, wherein the chondroitin sulfate has a weight average molecular weight of less than about 16.9 kilodaltons.
15
4. The method according to claim 3, wherein the chondroitin sulfate has a weight average molecular weight of less than about 10 kilodaltons.
20
5. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a cyclooxygenase-2 IC_{50} of less than about 0.2 $\mu\text{mol/L}$.
25
6. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least about 2.
30
7. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a cyclooxygenase-2 IC_{50} of less than about 0.2 $\mu\text{mol/L}$ and also has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least about 100.

8. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a cyclooxygenase-1 IC₅₀ of at least about 1 μmol/L.

9. The method according to claim 8, wherein the 5 cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a cyclooxygenase-1 IC₅₀ of at least about 10 μmol/L.

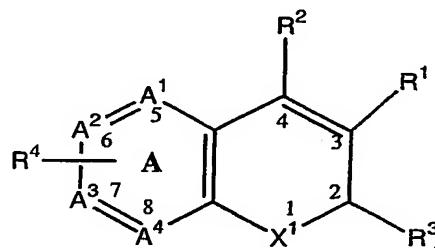
10. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises 6-[[5-(4-chlorobenzoyl)- 10 1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, having the formula:



or a prodrug thereof.

15 11. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a chromene.

12. The method according to claim 11, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes 20 having the general formula:



wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, $C_1 - C_3$ -alkyl, (optionally substituted phenyl)- $C_1 - C_3$ -alkyl, acyl and carboxy- $C_1 - C_6$ -alkyl;

wherein each of R^b and R^c is independently selected from hydrido, $C_1 - C_3$ -alkyl, phenyl- $C_1 - C_3$ -alkyl, $C_1 - C_3$ -perfluoroalkyl, chloro, $C_1 - C_6$ -alkylthio, $C_1 - C_6$ -alkoxy, nitro, cyano and cyano- $C_1 - C_3$ -alkyl; or wherein $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, $C_1 - C_6$ -alkylsulfonylaminocarbonyl and $C_1 - C_6$ -alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, $C_1 - C_6$ -alkyl and $C_2 - C_6$ -alkenyl;

wherein R^3 is selected from $C_1 - C_3$ -perfluoroalkyl, chloro, $C_1 - C_6$ -alkylthio, $C_1 - C_6$ -alkoxy, nitro, cyano and cyano- $C_1 - C_3$ -alkyl;

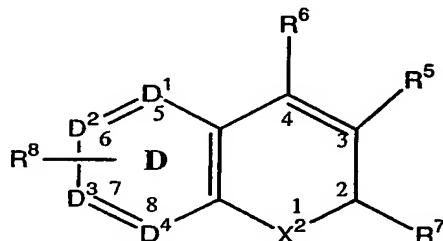
wherein R^4 is one or more radicals independently selected from hydrido, halo, $C_1 - C_6$ -alkyl, $C_2 - C_6$ -alkenyl, $C_2 - C_6$ -alkynyl, halo- $C_2 - C_6$ -alkynyl, aryl- $C_1 - C_3$ -alkyl, aryl- $C_2 - C_6$ -alkynyl, aryl- $C_2 - C_6$ -alkenyl, $C_1 - C_6$ -alkoxy, methylenedioxy, $C_1 - C_6$ -alkylthio, $C_1 - C_6$ -alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, $C_1 - C_6$ -alkoxy- $C_1 - C_6$ -alkyl, aryl- $C_1 - C_6$ -alkyloxy, heteroaryl- $C_1 - C_6$ -alkyloxy, aryl- $C_1 - C_6$ -alkoxy- $C_1 - C_6$ -alkyl, aryl- $C_1 - C_6$ -haloalkyl, $C_1 - C_6$ -haloalkoxy, $C_1 - C_6$ -haloalkylthio, $C_1 - C_6$ -haloalkylsulfinyl, $C_1 - C_6$ -haloalkylsulfonyl, $C_1 - C_3$ -(haloalkyl- $C_1 - C_3$ -hydroxyalkyl, $C_1 - C_6$ -hydroxyalkyl, hydroxyimino- $C_1 - C_6$ -alkyl, $C_1 - C_6$ -alkylamino, arylamino, aryl- $C_1 - C_6$ -alkylamino, heteroarylamino, heteroaryl- $C_1 - C_6$ -alkylamino, nitro, cyano, amino, aminosulfonyl, $C_1 - C_6$ -alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl- $C_1 - C_6$ -alkylaminosulfonyl, heteroaryl- $C_1 - C_6$ -alkylaminosulfonyl, heterocyclsulfonyl, $C_1 - C_6$ -alkylsulfonyl, aryl- $C_1 - C_6$ -alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl- $C_1 - C_6$ -alkylcarbonyl, heteroaryl- $C_1 - C_6$ -alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, $C_1 - C_1$ -alkoxycarbonyl, formyl, $C_1 - C_6$ -haloalkylcarbonyl and $C_1 - C_6$ -alkylcarbonyl; and

wherein the A ring atoms A^1 , A^2 , A^3 and A^4 are independently

selected from carbon and nitrogen with the proviso that at least two of A¹, A², A³ and A⁴ are carbon;

or wherein R⁴ together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl;
5 or an isomer or pharmaceutically acceptable salt thereof.

13. The method according to claim 11, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the general formula:



10

wherein X² is selected from O, S, CR^c R^b and NR^a;

wherein R^a is selected from hydrido, C₁ -C₃ -alkyl, (optionally substituted phenyl)-C₁ -C₃ -alkyl, alkylsulfonyl, phenylsulfonyl, 15 benzylsulfonyl, acyl and carboxy-C₁ -C₆ -alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C₁ -C₃ -alkyl, phenyl-C₁ -C₃ -alkyl, C₁ -C₃ -perfluoroalkyl, chloro, C₁ -C₆ -alkylthio, C₁ -C₆ -alkoxy, nitro, cyano and cyano-C₁ -C₃ -alkyl;

or wherein CR^c R^b form a cyclopropyl ring;

20 wherein R⁵ is selected from carboxyl, aminocarbonyl, C₁ -C₆ -alkylsulfonylaminocarbonyl and C₁ -C₆ -alkoxycarbonyl;

wherein R⁶ is selected from hydrido, phenyl, thiienyl, C₂ -C₆ -alkynyl and C₂ -C₆ -alkenyl;

25 wherein R⁷ is selected from C₁ -C₃ -perfluoroalkyl, chloro, C₁ -C₆ -alkylthio, C₁ -C₆ -alkoxy, nitro, cyano and cyano-C₁ -C₃ -alkyl;

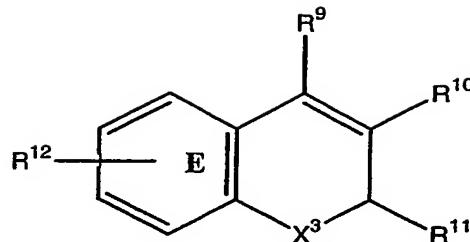
wherein R⁸ is one or more radicals independently selected from

hydrido, halo, C₁ -C₆ -alkyl, C₂ -C₆ -alkenyl, C₂ -C₆ -alkynyl, halo-C₂ -C₆ -alkynyl, aryl-C₁ -C₃ -alkyl, aryl-C₂ -C₆ -alkynyl, aryl-C₂ -C₆ -alkenyl, C₁ -C₆ -alkoxy, methylenedioxy, C₁ -C₆ -alkylthio, C₁ -C₆ -alkylsulfinyl, —O(CF₂)₂—O—, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C₁ -C₆ -alkoxy-C₁ -C₆ -alkyl, aryl-C₁ -C₆ -alkyloxy, heteroaryl-C₁ -C₆ -alkyloxy, aryl-C₁ -C₆ -alkoxy-C₁ -C₆ -alkyl, C₁ -C₆ -haloalkyl, C₁ -C₆ -haloalkoxy, C₁ -C₆ -haloalkylthio, C₁ -C₆ -haloalkylsulfinyl, C₁ -C₆ -haloalkylsulfonyl, C₁ -C₃ -(haloalkyl-C₁ -C₃ -hydroxyalkyl), C₁ -C₆ -hydroxyalkyl, hydroxyimino-C₁ -C₆ -alkyl, C₁ -C₆ -alkylamino, arylamino, aryl-C₁ -C₆ -alkylamino, heteroarylamino, heteroaryl-C₁ -C₆ -alkylamino, nitro, cyano, amino, aminosulfonyl, C₁ -C₆ -alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C₁ -C₆ -alkylaminosulfonyl, heteroaryl-C₁ -C₆ -alkylaminosulfonyl, heterocyclsulfonyl, C₁ -C₆ -alkylsulfonyl, aryl-C₁ -C₆ -alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C₁ -C₆ -alkylcarbonyl, heteroaryl-C₁ -C₆ -alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C₁ -C₆ -alkoxycarbonyl, formyl, C₁ -C₆ -haloalkylcarbonyl and C₁ -C₆ -alkylcarbonyl; and

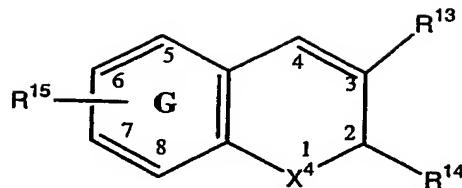
wherein the D ring atoms D¹, D², D³ and D⁴ are independently selected from carbon and nitrogen with the proviso that at least two of D¹, D², D³ and D⁴ are carbon;

or wherein R⁸ together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

14. The method according to claim 11, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the general formula:



- wherein X^3 is selected from the group consisting of O or S or NR^a ;
- wherein R^a is alkyl;
- wherein R^9 is selected from the group consisting of H and aryl;
- 5 wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxy carbonyl;
- wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and
- 10 wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, 15 arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or
- 20 wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof;
- and including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.
15. The method according to claim 11, wherein the
- 25 cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



wherein X^4 is selected from O or S or NR^a ;

wherein R^a is alkyl;

wherein R^{13} is selected from carboxyl, aminocarbonyl,

5 alkylsulfonylaminocarbonyl and alkoxy carbonyl;

wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

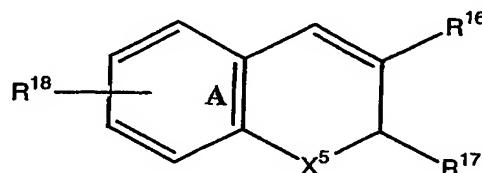
wherein R^{15} is one or more radicals selected from hydrido, halo,

10 alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroaryl amino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^{15} together with ring G forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

20 16. The method according to claim 11, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



wherein:

X^5 is selected from the group consisting of O or S or NR^b ;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

5 R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

10 R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylarnino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

15 or wherein R^{18} together with ring A forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof.

20 17. The method according to claim 16, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

25 R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing

- heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or
wherein R¹⁸ together with ring A forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof.
- 5 18. The method according to claim 16, wherein:
R¹⁶ is carboxyl;
R¹⁷ is lower haloalkyl; and
R¹⁸ is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower
10 alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl;
- 15 or wherein R¹⁸ together with ring A forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof.
19. The method according to claim 16, wherein:
R¹⁶ is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;
20 R¹⁷ is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and
R¹⁸ is one or more radicals selected from the group consisting of
25 hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropoxy, *tert*butyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl,

N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R² together with ring A forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof.

5

20. The method according to claim 16, wherein:

R¹⁶ is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;

R¹⁷ is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

10

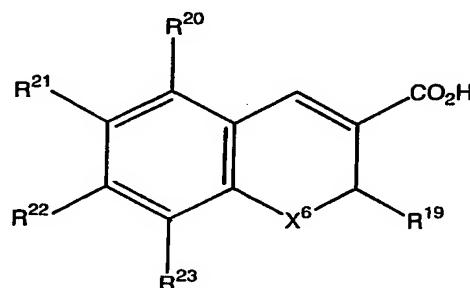
R¹⁸ is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl;

or wherein R¹⁸ together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

20

21. The method according to claim 11, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



wherein:

25

X⁶ is selected from the group consisting of O and S;

- 5 R^{19} is lower haloalkyl;
 R^{20} is selected from the group consisting of hydrido, and halo;
 R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

10 R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and
 R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;
or an isomer or prodrug thereof.

15 22. The method according to claim 21, wherein:
 X^6 is selected from the group consisting of O and S;
 R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;
 R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

20 R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

25 R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and
 R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;
or an isomer or prodrug thereof.

30 23. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises:

- a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;
- a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;
- a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;
- 5 a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;
- a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide
- 10 a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;
- a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- 15 a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- 20 b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide
- b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 25 b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 30 b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

- b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 5 c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 10 c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- 15 c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 20 d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;
- d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 25 d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- 30 d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

- d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
- d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- 5 e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
- e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
- e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
- 10 e4) 2-[(3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;
- e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- 15 e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;
- e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;
- e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
- 20 e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;
- e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
- 25 f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
- f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;
- f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 30 f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

- f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 5 f7) 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- 10 f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 15 g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
- 20 g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
- g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- 25 g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
- g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- 30 g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

- h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- 5 h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- 10 h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- 15 h10) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;
- i1) N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
- 20 i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
- i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
- i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
- 25 i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;
- 30 i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

- i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- 5 i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyoxy)-6-(trifluoromethyl)pyridine;
- j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
- 10 j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;
- j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;
- j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
- j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 15 j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;
- j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 20 k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- 25 k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-
- 30 yl]benzenesulfonamide;
- k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

- k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
- k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- 5 l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
- 10 l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
- 15 l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;
- l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;
- l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
- 20 l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
- m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
and
- m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.
- 25 m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;
- m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o4) 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
- o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

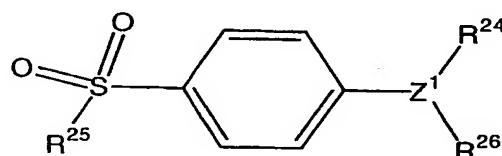
- o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 5 o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 10 p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p4) 6-[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 15 p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 20 p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 25 p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q1) 8-chloro-6-[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- 30 q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2*H*-1-benzopyran-3-carboxylic acid;
- q6) 6-benzylsulfonyl-2-trifluoromethyl-2*H*-1-benzopyran-3-carboxylic acid;
- 5 q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2*H*-1-benzopyran-3-carboxylic acid;
- q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2*H*-1-benzopyran-3-carboxylic acid;
- q9) 6-iodo-2-trifluoromethyl-2*H*-1-benzopyran-3-carboxylic acid;
- 10 q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2*H*-1-benzopyran-3-carboxylic acid;
- r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5*H*)-fluranone;
- r2) 6-chloro-2-trifluoromethyl-2*H*-1-benzothiopyran-3-carboxylic acid;
- 15 r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide;
- r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide;
- r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide;
- 20 r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine;
- r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1*H*-imidazol-2-yl]pyridine;
- 25 r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1*H*-imidazol-1-yl]benzenesulfonamide;
- r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
- 30 s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

24. The method according to claim 1, wherein the
5 cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



wherein:

10 Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

15 R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

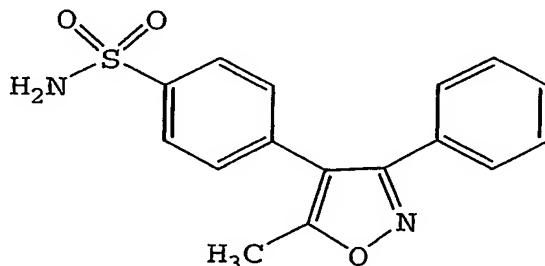
20 R^{25} is selected from the group consisting of methyl or amino; and

25 R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N- arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N- arylamino, N- aralkylamino, N-alkyl-N- aralkylamino, N-alkyl-N- arylamino,

aminoalkyl, alkylaminoalkyl, N-arylaminooalkyl, N-aralkylaminooalkyl, N-alkyl-N-aralkylaminooalkyl, N-alkyl-N-arylaminooalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

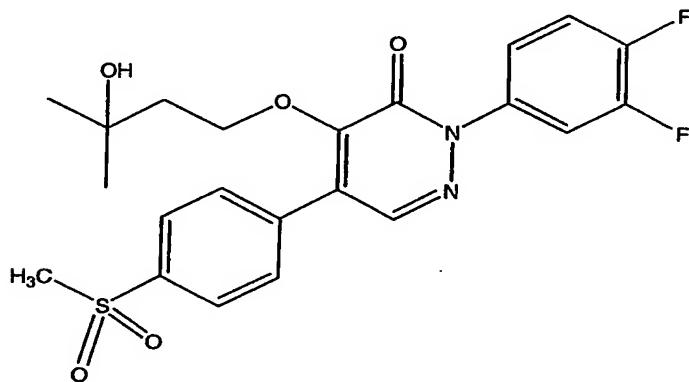
5 or a prodrug thereof.

25. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises valdecoxib, having the following formula:



10 or a prodrug thereof.

26. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



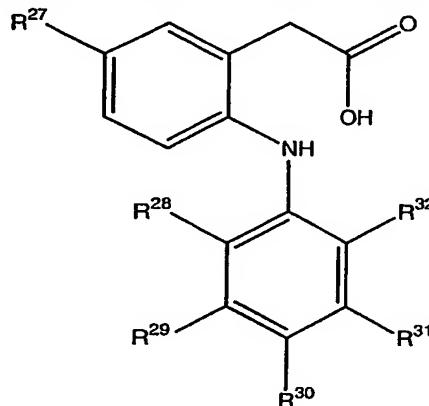
15 or a prodrug thereof.

27. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, JTE-522, deracoxib, a chromene, a chroman, parecoxib,

valdecoxib, etoricoxib, rofecoxib, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, COX189, ABT963, meloxicam, prodrugs of any of them, and mixtures thereof.

28. The method according to claim 27, wherein the
5 cyclooxygenase-2 selective inhibitor comprises celecoxib or a prodrug thereof.

29. The method according to claim 1, wherein the
cyclooxygenase-2 selective inhibitor comprises a phenylacetic acid derivative represented by the general structure:



10

wherein:

R²⁷ is methyl, ethyl, or propyl;

R²⁸ is chloro or fluoro;

R²⁹ is hydrogen, fluoro, or methyl;

15 R³⁰ is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R³¹ is hydrogen, fluoro, or methyl; and

R³² is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R²⁸, R²⁹, R³⁰ and R³¹ are not all fluoro when R²⁷ is ethyl and
20 R³⁰ is H;

or a prodrug thereof.

30. The method according to claim 29, wherein:

R²⁷ is ethyl;

R²⁸ and R³⁰ are chloro;

R^{29} and R^{31} are hydrogen; and
 R^{32} is methyl;
or a prodrug thereof.

31. The method according to claim 29, wherein:

5 R^{27} is propyl;
 R^{28} and R^{30} are chloro;
 R^{29} and R^{31} are methyl; and
 R^{32} is ethyl;
or a prodrug thereof.

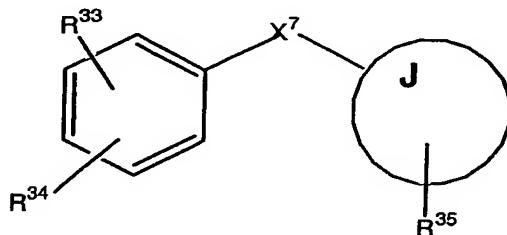
10 32. The method according to claim 29, wherein:

R^{27} is methyl;
 R^{28} is fluoro;
 R^{32} is chloro; and
 R^{29} , R^{30} , and R^{31} are hydrogen;

15 or a prodrug thereof.

33. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a diarylmethylidenefuran derivative.

34. The method according to claim 1, wherein the
20 cyclooxygenase-2 selective inhibitor comprises a compound having the general formula:



wherein:

25 X is O; J is 1-phenyl; R^{33} is 2- $NHSO_2CH_3$; R^{34} is 4- NO_2 ; and there is no R^{35} group, (nimesulide), and

X is O; J is 1-oxo-inden-5-yl; R³³ is 2-F; R³⁴ is 4-F; and R³⁵ is 6-NHSO₂CH₃, (flosulide); and

X is O; J is cyclohexyl; R³³ is 2-NHSO₂CH₃; R³⁴ is 5-NO₂; and there is no R³⁵ group, (NS-398); and

5 X is S; J is 1-oxo-inden-5-yl; R³³ is 2-F; R³⁴ is 4-F; and R³⁵ is 6-N⁺SO₂CH₃ · Na⁺,
(L-745337); and

X is S; J is thiophen-2-yl; R³³ is 4-F; there is no R³⁴ group; and R³⁵ is 5-NHSO₂CH₃, (RWJ-63556); and

10 X is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R³³ is 3-F; R³⁴ is 4-F; and R³⁵ is 4-(p-SO₂CH₃)C₆H₄, (L-784512).

15 35. A method of treating or preventing a cyclooxygenase-2 mediated disorder in a subject, said method comprising treating the subject having or susceptible to said disorder with a therapeutically-effective amount of a combination of chondroitin sulfate and a cyclooxygenase-2 selective inhibitor.

36. The method according to claim 27, wherein the cyclooxygenase-2 mediated disorder is selected from the group consisting of inflammation, arthritis, pain and fever.

20 37. The method according to claim 2, wherein the amount of chondroitin sulfate is within a range of about 5 to about 150 mg/day per kilogram of body weight of the subject.

25 38. The method according to claim 37, wherein the amount of chondroitin sulfate is within a range of about 10 to about 20 mg/day per kilogram of body weight of the subject.

30 39. The method according to claim 1, wherein the amount of cyclooxygenase-2 selective inhibitor or pharmaceutically acceptable salt or prodrug thereof, together with the amount of chondroitin sulfate, constitute an amount effective for the treatment, prevention, or inhibition of the pain, inflammation or inflammation-associated disorder.

40. The method according to claim 39, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a

range of from about 0.01 to about 100 mg/day per kg of body weight of the subject.

41. The method according to claim 40, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a 5 range of from about 1 to about 20 mg/day per kg of body weight of the subject.

42. The method according to claim 1, wherein the weight ratio of the amount of chondroitin sulfate to the amount of cyclooxygenase-2 10 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof that is administered to the subject is within a range of from about 0.05:1 to about 15,000:1.

43. The method according to claim 42, wherein the weight ratio of the amount of chondroitin sulfate to the amount of cyclooxygenase-2 15 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof that is administered to the subject is within a range of from about 0.15:1 to about 1000:1.

44. The method according to claim 43, wherein the weight ratio of the amount of chondroitin sulfate to the amount of cyclooxygenase-2 20 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof that is administered to the subject is within a range of from about 0.5:1 to about 20:1.

45. The method according to claim 1, wherein the pain, 25 inflammation or inflammation associated disorder is selected from the group consisting of headache, fever, arthritis, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, skin related conditions, psoriasis, eczema, burns, dermatitis, gastrointestinal conditions, inflammatory bowel disease, gastric ulcer, gastric varices, 30 Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, cancer, colorectal cancer, herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis,

5 candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarthritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, 10 polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, ophthalmic diseases, retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, acute injury to the eye tissue, pulmonary inflammation, nervous system disorders, cortical dementias, 15 and Alzheimer's disease.

10 46. The method according to claim 1, wherein the pain, inflammation or inflammation associated disorder is an ophthalmic associated disorder or ophthalmic injury that is selected from the group consisting of retinitis, retinopathies, conjunctivitis, uveitis, ocular 15 photophobia and acute injury to the eye tissue.

47. The method according to claim 45, wherein the pain, inflammation or inflammation associated disorder is osteoarthritis.

48. The method according to claim 45, wherein the pain, inflammation or inflammation associated disorder is rheumatoid arthritis.

20 49. The method according to claim 1, wherein the subject is an animal.

50. The method according to claim 49, wherein the subject is a human.

25 51. The method according to claim 1, wherein the treating step comprises administering chondroitin sulfate and a cyclooxygenase-2 selective inhibitor to the subject enterally or parenterally in one or more dose per day.

30 52. The method according to claim 1, wherein the chondroitin sulfate and the cyclooxygenase-2 selective inhibitor are administered to the subject substantially simultaneously.

53. A method for the treatment of a subject that has need of the treatment or prevention of disorders having an inflammatory component,

the method comprising administering to the subject a therapeutically effective dose of chondroitin sulfate and cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.

5 54. The method according to claim 1, wherein glucosamine is also present.

55. The method according to claim 54, wherein the glucosamine is present in an amount which, in combination with the amount of chondroitin sulfate and the amount of the cyclooxygenase-2 selective inhibitor, comprises a therapeutic amount.

10 56. The method according to claim 55, wherein the glucosamine is selected from the group consisting of glucosamine; glucosamine salts of hydrochloric, sulfuric, phosphoric, or other pharmaceutically acceptable acid; glucosamine-2-sulfate; glucosamine-3-sulfate; glucosamine-6-sulfate; glucosamine-2,3-disulfate; glucosamine-2,6-disulfate; glucosamine-3,6-disulfate; glucosamine-3,4,6-trisulfate; glucosamine pentaacetate; glucosamine-1-phosphate; glucosamine-6-phosphate; N-acetylglucosamine-6-phosphate; N-acetylglucosamine-1-phosphate; N-acetyl-D-glucosamine; uridine diphosphate (UDP)-N-acetylglucosamine; and mixtures thereof.

15 57. The method according to claim 54, wherein the glucosamine comprises hydrolysis products and other derivatives of chitin, hyaluronic acid, heparin, or keratosulfate which contain glucosamine or a derivative thereof.

20 58. The method according to claim 54, wherein the amount of glucosamine is within a range of from about 0.1 to about 500 mg/day per kg of body weight of the subject.

25 59. The method according to claim 58, wherein the amount of glucosamine is within a range of from about 15 to about 25 mg/day per kg of body weight of the subject.

30 60. A composition for the treatment, prevention, or inhibition or pain, inflammation, or inflammation-associated disorder comprising

chondroitin sulfate and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

61. A composition according to claim 60, comprising a combination of chondroitin sulfate and a cyclooxygenase-2 selective 5 selected from the group consisting of celecoxib, rofecoxib, deracoxib, valdecoxib, parecoxib, and etoricoxib.

62. A pharmaceutical composition comprising chondroitin sulfate; a cyclooxygenase-2 specific inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically-acceptable 10 excipient.

63. The pharmaceutical composition according to claim 62, wherein the chondroitin sulfate and the cyclooxygenase-2 selective inhibitor comprise a combination of chondroitin sulfate and a cyclooxygenase-2 selective inhibitor that is selected from the group 15 consisting of celecoxib, rofecoxib, deracoxib, valdecoxib, parecoxib, and etoricoxib.

64. A kit that is suitable for use in the treatment, prevention or inhibition of pain, inflammation or inflammation-associated disorder, the kit comprises a first dosage form comprising chondroitin sulfate and a second 20 dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder.

65. The kit according to claim 64, comprising a third dosage form 25 comprising glucosamine.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/25673

| A. CLASSIFICATION OF SUBJECT MATTER | | | | | |
|-------------------------------------|------------|--|-----------|------------|------------|
| IPC 7 | A61K31/737 | A61K31/42 | A61K31/50 | A61K31/501 | A61K31/415 |
| | A61P29/00 | //(A61K31/737, 31:42), (A61K31/737, 31:50), (A61K31/737, 31:501), (A61K31/737, 31:415) | | | |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| P, X | US 2002/086070 A1 (KUHRTS ERIC HAUSER) 4 July 2002 (2002-07-04) claims 1-18 --- | 1-65 |
| X | WO 01 41783 A (LEVIN BRUCE) 14 June 2001 (2001-06-14) page 7, line 6-9; claims 1-4 --- | 1-65 |
| X | MANEK N J: "Medical management of osteoarthritis." MAYO CLINIC PROCEEDINGS. UNITED STATES MAY 2001, vol. 76, no. 5, May 2001 (2001-05), pages 533-539, XP001118194 ISSN: 0025-6196 page 536, right-hand column, line 10-29 page 537, left-hand column, line 26 -right-hand column, line 12 --- | 1-65 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

22 October 2002

Date of mailing of the international search report

04/11/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patenttaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/25673

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------|
| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | <p>MILLER C A: "Newer and safer options for osteoarthritis." GERIATRIC NURSING (NEW YORK, N.Y.) UNITED STATES 2001 MAY-JUN, vol. 22, no. 3, May 2001 (2001-05), pages 165-166, XP001107069 ISSN: 0197-4572 the whole document</p> <p>-----</p> | 1-65 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/25673

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: - because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: - because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-59 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT – Method for treatment of the human or animal body by surgery

Continuation of Box I.2

The subject-matter of present claims 1-9, 35-56, 60, 62 and 64-65 is defined by means of the functional feature "COX-2 selective inhibitor" and similar wordings. Because of the character of the functional feature, it cannot be guaranteed that the performed search is complete. It cannot be excluded that compounds fulfilling the requirements of the functional feature have not been identified as soing so in the prior art. If such compounds have not been identified in the application either, they have not been covered by the search.

The search has been carried out, based on the functional feature as such as well as the expliccit examples given in the claims and the examples.

Present claims 10-24 and 29 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mrntionrf explicitly in the claims as well as in the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/25673

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|-------------------------------|--------------------------|
| US 2002086070 | A1 04-07-2002 | NONE | |
| WO 0141783 | A 14-06-2001 | AU 1953701 A WO 0141783 A1 | 18-06-2001 14-06-2001 |